DISSERTATION ON

A RANDOMIZED CLINICAL TRIAL COMPARING MIDAZOLAM AND PREGABALIN AS PREMEDICANTS IN ATTENUATING NEUROENDOCRINE STRESS RESPONSE DURING GENERAL ANAESTHESIA IN ELECTIVE SURGERIES

Dissertation submitted

in partial fulfillment of the regulations

for the award of the degree of

M.D.DEGREE BRANCH-X

ANAESTHESIOLOGY

of

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

ESI-POSTGRADUATE INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

KK NAGAR

CHENNAI

APRIL 2013

CERTIFICATE

This is to certify that this dissertation **"**A RANDOMIZED CLINICAL TRIAL COMPARING MIDAZOLAM AND PREGABALIN AS PREMEDICANTS IN ATTENUATING NEUROENDOCRINE STRESS RESPONSE DURING GENERAL ANAESTHESIA IN ELECTIVE SURGERIES**"** submitted by **Dr.BHAVANI.M,** appearing for M.D. Degree Branch X ANAESTHESIOLOGY examination in April 2013 is a bonafide record of work done by her under my direct guidance and supervision in partial fulfillment of the regulations of the Tamilnadu Dr.M.G.R Medical University, Chennai. I forward this to the Tamilnadu Dr.M.G.R Medical University, Chennai, Tamilnadu, India.

PROFESSOR AND HOD DEAN
Guide
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DECLARATION

I solemnly declare that this dissertation entitled "A **RANDOMIZED CLINICAL TRIAL COMPARING MIDAZOLAM AND PREGABALIN AS PREMEDICANTS IN ATTENUATING NEUROENDOCRINE STRESS RESPONSE DURING GENERAL ANAESTHESIA IN ELECTIVE SURGERIES"** was done by me at ESI-PGIMSR,KKNAGAR,CHENNAI during 2011-2013 under the guidance and supervision of **PROFESSOR Dr. KAMALINI SRIDHARAN MD., DA.** This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical Unviersity towards the partial fulfillment of requirements for the award of M.D. Degree in ANAESTHESIOLOGY (Branch-X).

Place : Chennai –78.

Date

Signature of Candidate

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CERTIFICATE OF APPROVAL

To

Dr. M. Bhavani
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ESI-PGIMSR, K.K.Nagar,
Chennai 600 078.

Dear Dr. Bhavani,

The Institutional Ethics committee of ESI-PGIMSR, reviewed and discussed your application for approval of the proposal entitled **"A Randomized clinical trial comparing Midazolam & Pregabalina as Premedicants in attenuating neuroendocrine stress response during General Anesthesia in elective surgeries"** No.1/02032012.

The following members of Ethics Committee were present in the meeting held on 02.03.2012 conducted at ESI-PGIMSR, Chennai 600 078.

1.	Dr. Saradha Suresh	-	Chairperson
2.	Dr. Kamalini Sridharan Prof. & HOD, Dept. Of Anesthesia, ESI-PGIMSR	-	Member Secretary
3.	Dr. Premila	-	EC Member
4.	Dr. N. Krishnan	-	EC Member
5.	Dr.K.S. Vijaya Raghavan	-	EC Member
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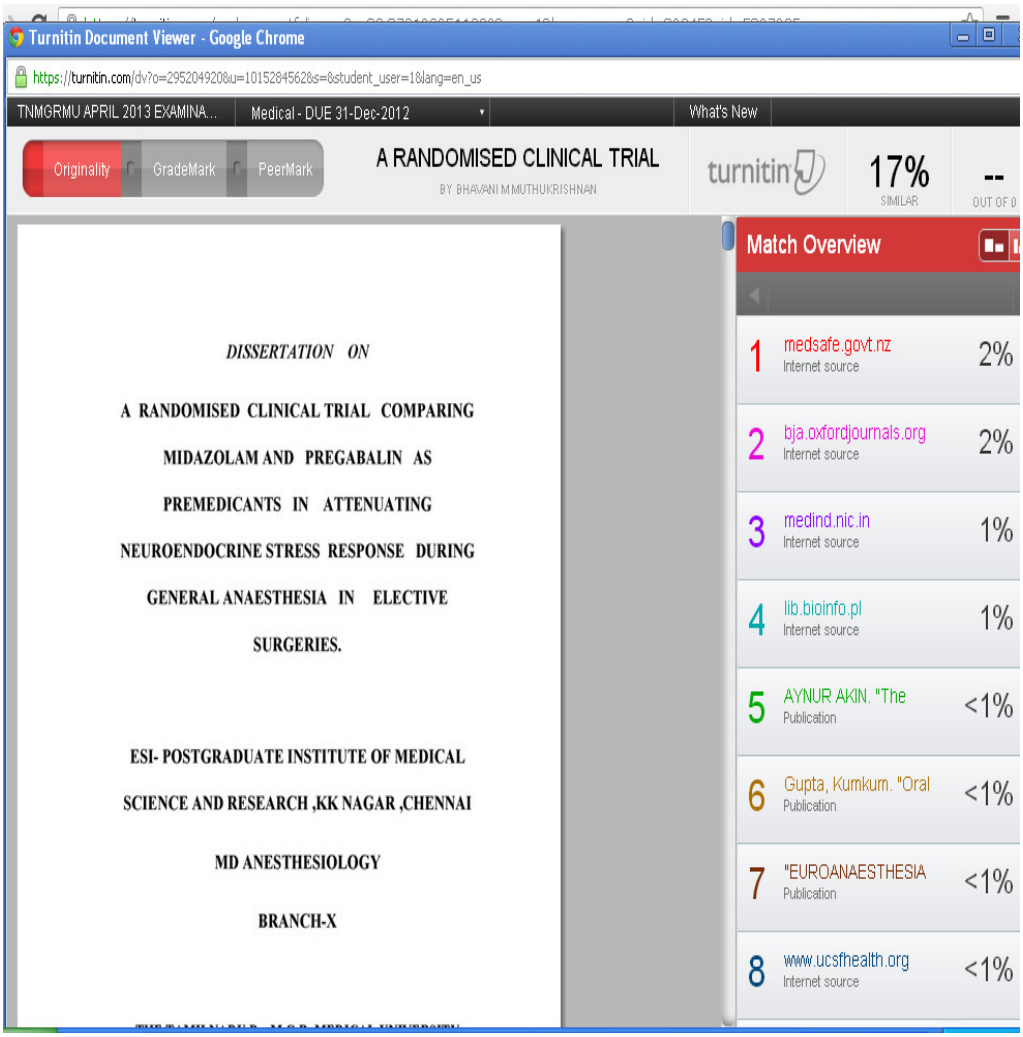
10.	Dr. A. Sundaram	-	EC Member
11.	Dr. Naganath Babu	-	EC Member
12.	Sister Lalitha Teresa	-	EC Member

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

Place : Chennai
Date : 02.03.2012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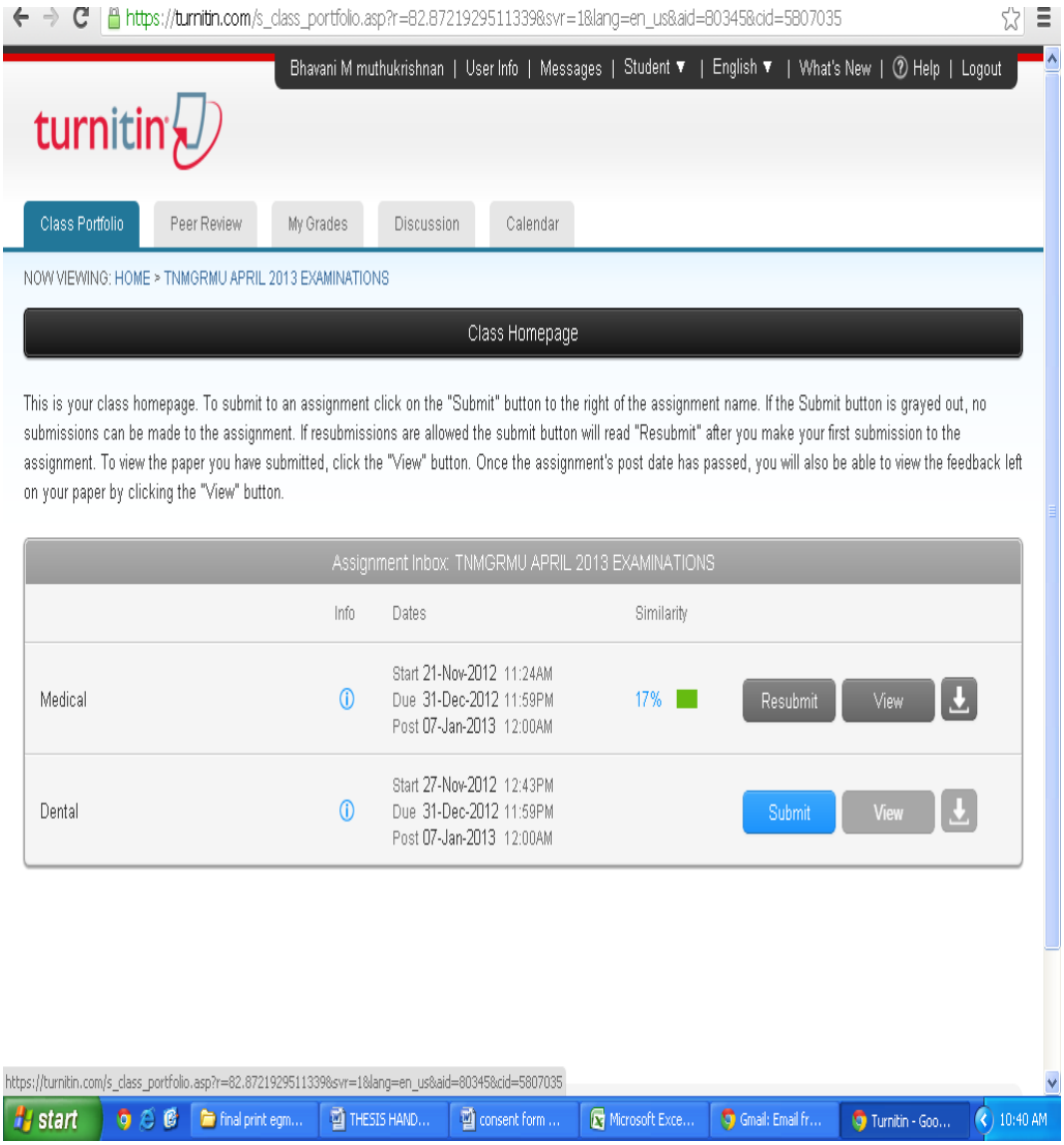
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CONTENTS

INTRODUCTION

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system. These changes due to the stress response have secondary effects on hormone secretion from other organs. For example, release of corticotropin from the pituitary stimulates cortisol secretion from the adrenal cortex. Arginine vasopressin which is secreted from the posterior pituitary has effects on the kidney. In the pancreas, glucagon is released and insulin secretion may be diminished. The overall metabolic effect of the hormonal changes is increased catabolism which mobilizes substrates to provide energy .The hormonal changes also lead to retention of salt and water to maintain fluid volume and cardiovascular homeostasis.

The changes triggered by the stress response are short-lived and well tolerated by normal healthy patients belonging to class 1 and 2 of American Society of Anaesthesiologist classification of Physical Status. In patients with other co-morbidities like myocardial ischemia, renal insufficiency, uncontrolled diabetes, liver disease and cerebrovascular diseases these changes can be life threatening.

HISTORY OF STRESS FREE ANAESTHESIA

Before 1846, highly stressful procedures like intra abdominal surgeries were not attempted at all . Rapper relates that surgical cases operated for longer than twenty minutes will cause death of the patients. He felt that intense pain would exhaust the patient's reserves.

The concept of reduction of perioperative stress to produce a beneficial effect on recovery was conceived by George .W.Crile (1864 - 1943).

Following that Harvey Cushing (1869 – 1939) combined regional blocks with ether anaesthesia to achieve smooth recovery . He used blood pressure measurement to mark the periods of stress during the surgery. Cushing confirmed that strict anaesthetic records maintained during surgery would prevent untoward events due to the stress response caused by surgery.

In 1957 P. Woodbridge and M. Pinsker defined general anaesthesia as

1) Paralysis

2) Unconsciousness

3) Attenuation of stress response

In 1947, Michael Roizen found out that eventhough general anaesthesia can prevent movement during surgery, it may not combat the sympathetic response to skin incision without the help of local anesthesia.

Edward Lowenstein used large doses of morphine for hemodynamic stability during cardiac surgery .

In 1967 short acting opioids,like fentanyl were used by Stanley instead of large doses of morphine to prevent the side effects of histamine release due to morphine .

In 1959, neuroleptanaesthesia was introduced by De Castro using opioids and tranquilizer to achieve stable hemodynamics during surgery. During the past years a series of studies to identify markers of stress response have been conducted. Significant elevation

in catecholamines , adrenocorticotropic hormone, cortisol, antidiuretic hormone and growth hormone were found to occur.

In patients who were given anaesthesia with agents like ether, the catabolic state produced by the stress hormones contributed to delayed recovery especially after major surgeries .

Lundy's balanced anesthesia combining several drugs was an important milestone in the development of strategies to attenuate the stress response .

The pre - anaesthetic screening plays an important role in identifying and quantifying the co-existent diseases and makes way for optimization of the same . The recognition of the factors which initiate the stress response can be considered for modification in the pre-operative period itself. Various anesthetic techniques and pain management strategies have been put into use to control the stress response. Certain drugs like anxiolytic drugs, beta-blockers, anti-hypertensives and anti anginal drugs are administered preoperatively to combat the illeffects of the stress response .

Even from very early times anesthesiologists have relied on the hemodynamic variables such as heart rate and blood pressure to assess

the autonomic responses to surgery and stress. Thereafter various tests to assess the neurohumoral outflow due to the stress response were deviced.

The catecholamines released due to stress cannot quantify for the level of stress response because of the individual variation seen in the way each individual reacts to the circulating catecholamines.

Thus the importance of attenuating the stress response is well evident and our study aims to compare the effects of oral Midazolam and oral Pregabalin in attenuating the neurohumoral stress response by estimating the serum cortisol levels.

AIM OF THE STUDY

A Randomised Clinical Trial comparing Midazolam and Pregabalin as premedicants in attenuating neuroendocrine stress response during General Anaesthesia in Elective Surgeries.

OBJECTIVE OF THE STUDY

Primary Objective:

To study the pattern of rise in serum cortisol levels during surgery in two groups of patients after premedicating one group with oral Midazolam and another with oral Pregabalin **.**

Secondary Objective:

To evaluate the changes in

- serum prolactin
- Plasma glucose
- The hemodynamic parameters like heart rate and blood pressure.

Primary outcome measure : Serum cortisol

Secondary outcome measure : Serum prolactin, plasma glucose, Heart rate and blood pressure.

REVIEW OF LITERATURE

Cuthbertson et al in 1932, described in detail the metabolic stress responses in four patients with lower limb injuries. Desborough et al[1] says that stress responses refer to the humoral and metabolic changes following injury or trauma .The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic system.

In the review article ,Dr Manorama Singh[2] quotes that hypotension, hypoxia, hypercarbia, acidosis, anxiety, emotion ,temperature, anesthetic factors like drugs, laryngoscopy, pain,light plane of anaethesia and surgical factors like duration of surgery, extent of tissue handling are the stimuli triggering the neuro-endocrine reflexes .

The mediators of all these responses have been studied from time immemorial. Literature search takes us way back into the 1970s when various interventions were tried in attenuating the responses. For triggering such a response a complex interplay of substances between the hypothalamic pituitary axis ,the neuroendocrine system and the

autonomic nervous system occurs. It results in hypermetabolism and acceleration of most of the biochemical reactions so when the stress response is prolonged substrate mobilization and immunosuppression occurs leading to increased morbidity and mortality.

In current anesthesia practice , no objective measurements for nociception or surgical stress exists. Inadequate analgesia during general anaesthesia may present as undesirable hemodynamic responses.

For instance ,in 1990 Huiku et al[3] reported that the intraoperative changes in blood cortisol and prolactin during surface surgery using total intravenous anaesthesia in forty ASA 1-2 patients Serum cortisol levels rose 30 minutes after extubation and serum prolactin increased in three situations after skin incision, extubation and 24 hours after surgery.

Blood levels of cortisol and prolactin were studied by Riverso etal[5] in twenty patients under going general anaesthesia under total intravenous and balanced anesthesia technique. Both increased the serum cortisol levels but the increase in the total intravenous technique was more .

Deborah etal[6] in their article have clearly outlined the mechanism of injury caused by the mediators like cortisol and that it correlated well with the severity of the insult and the response is not abolished by the administration of corticosteroids.

Chana et al [7] reported that the rise in serum cortisol was independent of age, sex ,length of surgery and ana esthetic technique also they added that rise in serum prolactin was more in females and there was significant post induction surge.

Barker et al [8] reported that since the cortisol increase is maximum during first four to six hours of the surgery,a series of samples are required to assess the pattern of rise in serum cortisol in a study comparing local and general anaesthesia for cataract surgery in a group of diabetic patients.

In another study by Zlata et al[9], serum cortisol and prolactin were measured thirty minutes before and after induction,after extubation and 24 hours after sugery in a group of 50 patiens under going lower abdominal surgeries and they found cortisol was elevated after extubation.

Nicholson et al[10] says that the amount of cortisol secreted following major surgery such as abdominal or thoracic surgery is between seventy five and hundred milligrams on the first day. The endogenous cortisol production is between 25 and 30mg per day,circulating in a circadian pattern and the half life is between 60 and 90 min. Plasma cortisol increase rapidly in response to surgery, peak values achieved within 4-6 hours,returing to normal after 24 hours.

Unase et al[11] reported,they found low cortisol levels in patients undergoing anorectal surgeries under saddle block than in general anaesthesia.

So, general anaesthesia itself is a strong stimulus for increasing serum cortisol and methods for attenuating this response have been done for ages. So this study intended to study the humoral, metabolic and hemodynamic responses during general anaesthesia after administering tablet Pregabalin 150mg or tablet Midazolam 7.5mg orally one hour before surgery.

Huncho etal[12], In 1992 reported that in two groups of patients undergoing total abdominal hysterectomy and general anaesthesia

with or without epidural blockade , serum prolactin concentration were increased during and after the surgery in both groups. While cortisol levels were low in the second group.

George et al[13] in their study mentioned that plasma catcholamines did not cause any significant change before, during or after the procedure. Most of the studies reported assessed the hemodynamic parameters associated with stress response.

Seyed etal[14] in another study found clonidine and gabapentin to blunt hemodynamic responses during intubation. They compared clonidine 200mcg with 900mg oral gabapentin as premedication 120 minutes before operation, with a placebo. They concluded that both clonidine and gabapentin have effective role in blunting hyperdynamic responses after laryngoscopy, more so with gabapentin.

So, many techniques were tried to attenuate the neuroendocme stren response as like in the above studies. All these literature searches led to further searches into finding a drug that could really be as effective as a premedicant in attenuating the neuroendocrine response.

Kain et al[15] reported that, postoperative outcomes were good in patients given midozolam ,those treated with midazolam preoperatively self-report improved postoperative recovery.

McEvoy etal[16] reported that, T.Midazolam is reviewed in the Hazardous Substances Database of National Library of Medicine. It states that Midazolam Hydrochloride is absorbed rapidly from the GI tract, with maximum plasma concentrating usually occurring within 1 hour.

Bailey etal[17] reported that respiratory depression may be caused by potentiation when administered along with opioids.

Likman-Mui etal[18] reported that many other studies highlighted that the benefits of Midazolam where the anxiety score was less in patients undergoing upper Gastro Intestinal scopy when treated with 7.5mg oral Midazolam.

Heine etal[19] reported that, also in another study in patients undergoing intraocular surgery using retrobulbar anesthesia, even though Midazolam led to higher sedation scores than placebo only one was deeply sedated. In patients who received low dose midozolam no increase in leucocyte number occurred. It has been shown that

retrobulbar anesthesia doubles plasma adrenaline levels which can be modified by oral low dose Midazolam.

SG Danle et al[20] in his article has concluded that oral Midazolam at 0.5mg/kg in children had better anxiolysis and smooth recovery.

Biro et al[21] reported , that a dose of 7.5mg Midazolam showed the best relation between desirable and undesirable effects.

Ravitsky et al[22] reported that Midazolam offers the benefits of balanced anesthesia, reduced alertness ,and reduced blood pressure with no clinically significant adverse events.

Lisa et al[23] reported that, in a study comparing oral clonidine 4mg/kg and oral Midazolam as preanaesthetic medications in the pediatric tonsillectomy patient, recommended the preferential use of Midazolam as a preanaesthetic medication in children undergoing tonsillectomy because Clonidine did not offer a better recovery profile.

Kumkum Gupta et al [24] reported that, the attenuation of hemodynamic responses to intubation using Pregabalin and Clonidine and they found both were effective premedicants. They also stated

that since there was no respiratory depression it may be used in asthmatics .

Agarwal et al[25] suggest that oral preoperative single dose of Pregabalin 150mg is an effective method for reducing postoperative pain and opioids consumption in patients undergoing laparoscopic cholecystectomy.

Elinor Ben-Menachan[26] has reported that Pregabalin does not bind to plasma proteins and not subject to hepatic metabolism,. Ashokkumar[27] et al reported that the preoperative use of Pregabalin shortens the time to achieve effective range of movements in the knee joint .

Rastogi[28] et al reported that oral pregabalin premedication attenuated the pressor response after air way instrumentation in a dose-related fashion and 150mg per dose was found to be optimal.

Baidya etal[29] reported that there is no clear evidence that the perioperative use of Pregabalin reduces postoperative pain intensity. It exihibits significant opioid sparing effects effects like vomiting. Schulmeyer et al [30] supported the same.

Sundar et al[31] studied the effects of premptive Pregabalin on attenuation of stress response to endotracheal intubation and opioid sparing effect in patients undergoing off pump coronary artery bypass grafting. The catecholamine secretion was not decreased.They concluded that it is not the plasma concentration of catecholamine that did matter but it was the reactivity to catecholamine that really counts.

When this is the case,serum cortisol estimation seems to be a better indicator for postoperative outcomes after administration of general anaesthesia.

The safety of both Midazolam and Pregabalin have been validated in the literature search and they have worked well as far as the hemodynamic response is concerned and our study tried to find out the hormonal influences of the premedicants.

THE METABOLIC STRESS RESPONSE

The metabolic stress response to surgical stress differs from that of starvation. Instead of preserving bodymass that occur during starvation,surgical stress causes “auto-cannibalism ”. This may result in loss of fat due to lipolysis and loss of lean body mass due to proteolysis.

In patients under stress the glucose uptake into the cell is limited by insulin resistance. So despite normal glucose oxidation pathway, gluconeogenesis is activated leading to hyperglycemia.

Stress causes immunodepression, recurrent infection and impaired wound healing.

Granulocytosis and thrombocytosis occur in response to increase in interleukin-6 and acute phase reactants. Decreased fibrinolysis due to reduced tissue plasminogen activator and increased plasminogen activator inhibitor is also found. Both procoagulant state and decreased fibrinolysis may predispose to deep vein thrombosis and pulmonary emboli in the postoperative period.

The secretion of acute phase reactants is stimulated by increased endogenous corticosteroid.

ILLEFFECTS OF STRESS HORMONES:

Increase in cardiac output occurs due to vasoconstriction of the peripheral and splanchnic vessels while vasodilatation occurs in coronary and cerebral vessels.

Increase in heart rate, blood pressure, myocardial contractility increases oxygen demand.

The respiratory rate also increases.

Sodium and water retention occurs resulting in decreased urinary output.

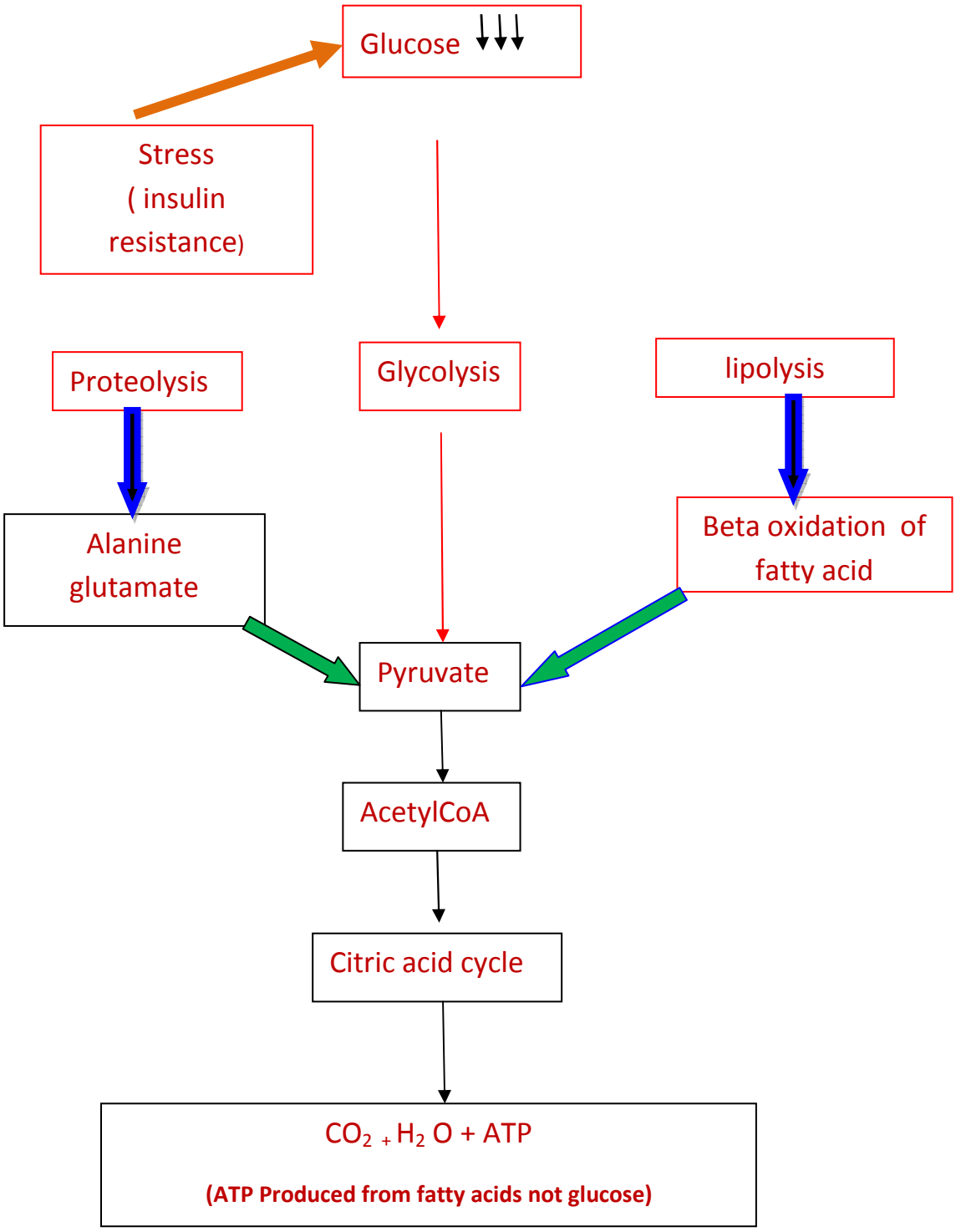
Immunosuppression predisposes to infection.

Substrate mobilization causes protein breakdown and hyperglycemia leading to weight loss.

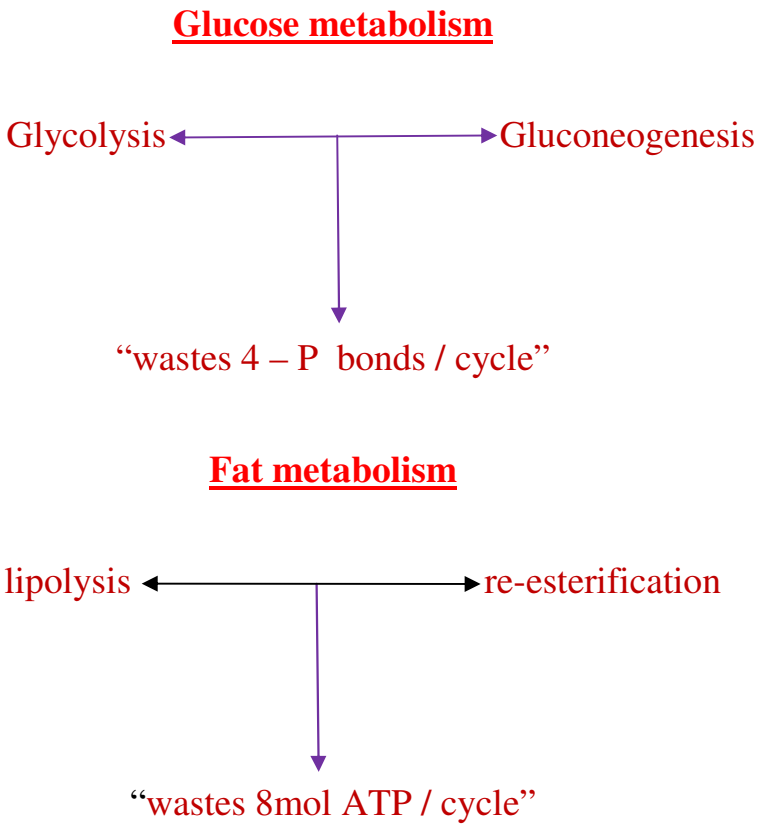
Coagulation problems may cause serious complications.

The following flow chart gives the metabolic mileu during stress resulting in hyperglycemia , lipolysis and proteolysis.

STRESS AND METBOLISM



LOSS OF ENERGY RICH BONDS



The alterations that occur in the metabolism of glucose , protein and fat cause wastage of the energy rich phosphate bonds which increases the metabolic requirements in the postoperative period. A patient who is nil per oral and who is dependent entirely on intravenous infusions may find it difficult to replenish the exhausted resources.

The intensity of the stress response depends on

- Duration of operation,
- Degree of injury ,
- Amount of blood lost during the procedure
- Intensity of postoperative pain .

Following the secretion of cortisol, an increase in levels of leptin and acute phase reactants occur especially in the levels of C- reactive protein.

Recent evidence suggests that salivary cortisol estimation as a non ivasive and reliable method for assessing the stress response. The salivary cortisol seems to increase within few minutes and shows good correlation with the serum levels.

THE TRIGGERS OF STRESS RESPONSE AND THE STRESS HORMONES

THE STIMULUS FOR STRESS RESPONSE:

Hypoxia , Hypotension , profound hypothermia, induction, intubation, extubation,light plane of anaesthesia, unneutralised pain, surgical manipulation, intraoperative complications, wound healing and inflammation.

THE PATHWAY:

The stimuli travel to the limbic system and from there to the posterior hypothalamus. The posterior hypothalamus controls the release of various hormones from pituitary like Arginine vasopressin, adrenocorticotropic hormone and aldosterone .They in turn release cortisol and catecholamine through the stimulation of the adrenals and the autonomic nervous system. This causes rise in heartrate, blood pressure and glucose levels.

Corticotrophin (ACTH) is a 39 amino acid peptide, produced in the pituitary from its precursor, pro‑opiomelanocortin.. Surgery is one of the most potent activators of Corticotropin which stimulates the adrenal cortex to secrete cortisol and high plasma concentrations

of both hormones can be found immediately after the initiation of surgery .

Decrease in growth hormone also occurs . The stress also interferes with the normal activity of thyroid hormones leading to symptoms of hypothyroidism .

The stress response can be either acute or chronic.The acute stress response and chronic response to stress differs in the amount of growth hormone secreted.

MODULATION OF THE STRESS RESPONSE

Though the stress response can result in adverse metabolic events , they are useful during situation of hypovolemia and hypotension which may occur during the surgery.The catecholamines are needed for maintaining blood pressure to ensure end- organ perfusion**.**

THE PREOPERATIVE PERIOD

The main goal of preoperative medication is to decrease the anxiety of surgery nonpharmacological methods like music , benzodiazepines like Midazolam, opioids like fentanyl have been known to modulate the preoperative stress response .

INTRAOPERATIVE PERIOD

The intraopertative stress response can be modulated by balanced anaesthesia and refined surgical techniques like laproscopy .

Volatile anaesthetics are ineffective in counteracting the metabolic response.The intravenous anaesthetics like propofol and etomidate have better control over the metabolic response than thiopentone sodium . Alpha $_2$ adrenergic agonist like clonidine and dexmedetomidine are more successful in attenuating the

hemodynamic and catecholamine response. Opioids are capable of decreasing hemodynamic and cytokine response but failed to decrease the catecholamines during cardiopulmonary bypass.

Advantages of regional anaesthesia over general anaesthesia

General anaesthesia makes the patient insensitive to pain and discomfort of surgery but it cannot abolish the afferent nervous input at the site of injury. Together it cannot antagonize the effects of interleukin-6 and tumour necrosis factor produced locally.

Regional anaesthesia is reported to be superior to general anaesthesia in preventing the stress response .It depends on the level of blockade, location of surgery and the drugs used. Lack of stimulation of hepatic glycogenolysis occurs due to reduced catecholamine response as seen in lumbar neuraxial anaesthesia. Continuous spinal techniques score better than thoracic epidural technique because vagal afferent nerves are not blocked in epidural anaesthesia .

The drugs like chloroprocaine and bupivaccine are found to decrease catecholamine response than lignocaine .

ROLE OF THERMO REGULATION

Maintaining perioperative normothermia is another way of minimizing the stress response . Hypothermia elevates serum catecholamines due to shivering and vasodilatation which can even result in serious events like myocardial ischemia .

POSTOPERATIVE PERIOD

In this period extreme elevations of plasma ACTH and cortisol are found suggesting that emergence from anaesthesia is a potent trigger of stress response . Many agents failed to suppress this response. Literature search leads us to the conclusion that very few agents can really blunt the postoperative response . Continuous epidural analgesia ensuring a pain free emergence was found to be successful in preventing the catecholamine surge but failed to decrease the metabolic response . Beta blockers cause end organ blockade and thereby reduce the metabolic response. Steroids when given sixty to ninety minutes before the onset of surgery was found to attenuate the cytokine secretion.

CONTROL OF GLUCOSE

Acute hyperglycemia is to be prevented because it leads to increased infection rates , reduced graft success and osmotic dieresis leading to volume depletion. The beneficial effects of lowering this hyperglycemia with strategies like insulin therapy are attributed to the concomitant decrease in proinflamatory reactants.

It is evident now that only a multimodal approach can be successful in attenuating catecholamine, neurohumoral and immunologic responses altogether . Miller ‘s textbook of anaesthesia highlights a schema for this multimodal intervention.

- Premedication
- Preoperative carbohydrate intake
- Intraoperative glycemic control
- Normothermia
- Neuraxial techniques and non steroidal anti-inflammatory drugs instead of opioids for pain relief
- Avoiding early feeding and parenteral nutrition
- early mobilization and non invasive surgery

With this in mind we were able to arrive at the hypothesis that any intervention in the preoperative period can be a good option to attenuate the stress response.The preoperative period is the one during which the patient can be counselled easily.They are in the most optimal state of the perioperative period atleast in elective surgeries .

We also thought of comparing two drugs one an analgesic and another a sedative so that we can findout whether pain relief or sedation would be a better intervention in attenuating the stress response.

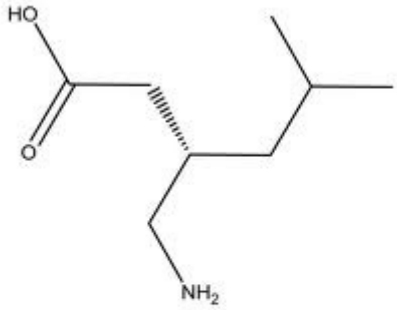
MIDAZOLAM Is a short acting ,water soluble benzodiazepine with good bioavailability when given orally and has been used for producing anxiolytic effect and anterograde amnesia. Also it is found to have analgesic effect when given intrathecally or in caudal epidural.

More recently antiepileptic drugs have been used for the treatment of acute postoperative pain and to reduce the postoperative analgesic requirements. PREGABALIN is effective in preventing neuropathic pain .It is well absorbed after oral administration and well tolerated with limited side effects . It does not have any significant

drug interactions. Pregabalin undergoes negligible hepatic metabolism and eliminated unchanged by renal excretion.

After getting convinced with the fact that Midazolam and pregabalin were suitable agents for our study a protocol was drawn and sent for approval of ethical committee . After the committee's approval our study was started.

PREGABALIN



Pregabalin

(S)-3-(Aminomethyl)-5-methylhexanoic acid

PHYSICAL AND CHEMICAL PROPERTIES

S-(+)-3-isobutylgaba, analogue of GABA

MECHANISM OF ACTION

It binds to alpha2-beta subunit of presynaptic, voltage-dependent calcium channels that are present in the central and peripheral nervous system. Reduces the release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, and substance P. Pregabalin is inactive at $GABA_A$ and $GABA_B$ receptors.

PHARMACOKINETICS:

ABSORPTION:

It is rapidly absorbed after oral ingestion in empty stomach, maximum plasma concentration occuring in one hour in the dose of 150mg/day.

ELIMINATION HALF LIFE**:** 6.3 hours

METABOLISM AND EXCRETION:

Pregabalin undergoes negligible metabolism in humans and is excreted unchanged by the kidneys. Pregabalin does not bind to plasma proteins.

PHARMACODYNAMICS:

Reduces the sensitization of dorsal horn neurons thereby reducing onset of chronic pain. Rapidly crosses the blood brain barrier.Reduces the communication between the nerves and this effect makes it a good antiepileptic.

ROUTES OF ADMINISTRATION:

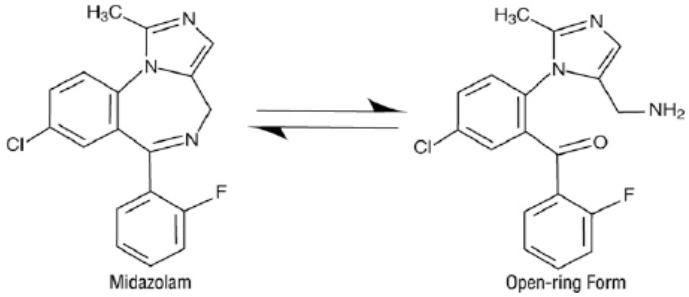
Oral tablets : dose:50-600 mg/day

Adverse effects/Precautions**:**

Dizziness, drymouth,edema, reduced blood platelet counts, increased blood creatinine kinase levels, rhabdomyolysis, muscle pain, weakness.

Contraindication: Nil, except hypersensitivity to the drug.

MIDAZOLAM



PHYSICAL AND CHEMICAL PROPERTIES :

Available as Midazolam maleate in the strength of 7.5 mg .

Chemically, midazolam maleate is is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazole[1,5-a][1,4] benzodiazepine maleate.

In pH of 5 to 8 open-ring form becomes physiologically active, lipophilic, closed-ring form .

MECHANISM OF ACTION:.

Like other benzodiazepines, the effects of Midazolam are mainly mediated via $GABA_A$ receptors at the limbic, thalamic, and hypothalamic levels. They produce anxiolysis, sedation, hypnosis, skeletal muscle relaxation, and anticonvulsant effects.

Benzodiazepines do not directly activate $GABA_A$ receptors, but require the endogenous ligand, GABA to exert the effects.

PHARMACOKINETICS

ABSORPTION

Midazolam is absorbed rapidly and completely after oral administration. Due to the substantial firstpass effect, bioavailability of oral Midazolam is between 30-70%. It gets rapidly redistributed in the tissues. 96-98% of Midazolam is bound to plasma proteins mainly to albumin. The relatively short duration of action of Midazolam is due in part to its very high metabolic clearance and rapid rate of elimination.

METABOLISM

Midazolam is almost entirely eliminated by biotransformation. Less than 1% of the dose is recovered in urine as the unchanged substance. Midazolam is hydroxylated by cytochrome isozymes in liver into two main metabolites: 1'-hydroxymidazolam and 4-hydroxymidazolam. 60-80% of the dose is glucuronidated and excreted in the urine in the form of the 1'-hydroxymidazolam conjugate. Plasma concentrations of 1'-hydroxymidazolam may

reach 30-50% those of the parent compound. 1'-hydroxymidazolam is pharmacologically active and contributes significantly (about 34%) to the effects of oral midazolam. Approximately 2-10% of an oral dose is excreted in feces.

ELIMINATION: The elimination half-life of Midazolam ranges between 1.5 to 2.5 hours

PHARMACODYNAMICS

Midazolam slowly crosses into cerebrospinal fluid. In humans, Midazolam has been shown to cross the placenta slowly and to enter fetal circulation, small quantities of Midazolam are secreted in human milk. It causes minimal haemodynamic changes.

DOSE: 5mg to 15 mg tablets.

CONTRAINDICATIONS

Severe respiratory insufficiency, Severe hepatic insufficiency; Sleep apnea syndrome; Children; Use in patients with known hypersensitivity to benzodiazepines , Myasthenia gravis.

CORTISOL

It is a steroid hormone released from the adrenal gland in response to ACTH, which is secreted from the pituitary gland in the brain.

It is a glucocorticoid and it is also known as hydrocortisone.

Normal serum values peak at 8.00 am around 6 to 23 mcg/dl Cortisol levels rise and fall during the day. The highest levels are seen at 6.00 - 8.00 a.m and the lowest at midnight. Daily around 20mg is produced but is capable of producing 150 to 300 mg per day.

This circadian rhythm of rise and fall of cortisol is vital for normal cognitive function, metabolic activity and immunomodulation. It stimulates hematopoiesis, induces liver enzymes, increases free water clearance.

For cortisol to exert only beneficial effects, the relaxation response following cortisol surge is mandatory. When there is a sustained increase it can cause impaired cognition , dyslipidemia , osteopenia , hyperglycemia and immunosuppression . Chronic increase impairs somatic growth by decreasing the growth hormone.

PROLACTIN

It is a protein hormone which has aminoacids similar to growth hormone. It is increased during stress response to surgery but it has only a minimal effect on the body functions . Basically it increases during pregnancy and controls lactation. It shows diurnal variation with the peak during REM sleep and seasonal changes . It is decreased during ovulation .

BLOOD GLUCOSE:

Usually there is an increase in blood glucose as soon as the surgical insult starts due to the effect of cortisol and catecholamines This facilitates glucose production by increased hepatic glycogenolysis and gluconeogenesis. Also there is increased peripheral resistance to insulin and to glucose utilization. Prolonged hyperglycemia can cause impaired wound healing and predispose to infection in the perioperative period.

REFERENCE VALUES:

These are the reference values given in our laboratory

Serum cortisol : - 6.7 to 22.6 mcg/dl (A.M)

2.9 – 17.3 mcg/dl(P.M)

Serum prolactin : - 3.34 -22.6 ng/ml. (males)

2 -29 ng/ml. (nonpregnant female)

20 -109 ng/ml. (pregnant female)

Random blood glucose : 70 to110 mg/dl

MATERIALS AND METHODS

INCLUSION CRITERIA:

Patients who were willing to participate

Age: 18 to 55 years

American Society of Anaesthesiologist Class 1 and II

Elective surgical procedures under general anaethesia

Duration of surgery : 30 minutes and 180 minutes.

EXCLUSION CRITERIA:

Preexisting co-morbidities [cardiac disease, diabetes, asthma, hepatic and renal dysfunction]

anticipated difficult intubation,

obesity,

epileptics,

pregnant patients,

patients on antidepressants .

After identifying the eligible patient, they were counselled on the day prior to sugery and separate consent got for the participation in the study .

Those patients in whom more than one intubation attempt was required or laryngoscopy and intubation took more than 45 seconds were also considered as difficult airway.

All menstruating women were tested for pregnancy using card test. Antidepressants can interfere with catecholamines ,so those patients on antidepressants were also excluded.

Those with baseline abnormalities in the lab values were also excluded.

PROCEDURE:

All consented patients , fulfilling the inclusion criteria were selected and divided into two groups .Group A received oral Midazolam 7.5 mg, Group B oral pregabalin 150 mg 60-90 minutes before surgery with sips of water (30-50 ml). They were randomly allocated to a particular group using computer generated numbers . The ward staff nurse administered the drug kept in sealed envelopes. For uniformity all premedicated patients were assigned as first case in the operative list . Both the patients and the person administering anaesthesia were unaware of the group. The details of the study were explained to the participants in their own language and informed consent was obtained on the day prior to surgery.

In the preoperative ward selected patients' first blood sample was collected around 8.00 am.since based on the circadian rhythm the cortisol levels come to a peak level around 8' o clock in the morning. For all the cases posted for surgery blood was drawn for grouping and crossmatch on the morning of surgery , so along with that an extra 2 ml **[baseline sample**] was drawn . After administration of the drug one hour before surgery patients' vitals were monitored and given oxygen supplementation if SPO2 falls below 95%. They were

brought to the operation theatre in a stretcher accompanied by medical/paramedical personnel. Inside the theatre the patients were connected to the monitors and an intravenous cannula was put . Simultaneously 2 ml blood **[second sample]** was drawn and a crystalloid infusion of 6-8 ml/kg/hr was started.

The anaesthetic technique was standardized in all patients. They were premedicated with Inj Glycopyrolate (10 mcg/kg), Inj Pentazocine[0.5 mg/kg] intravenously . After preoxygenation for five minutes they were induced with Inj Thiopentone[5mg/kg] , intubation facilitated with Vecuronium(0.15mg/kg) and appropriate size endotracheal tube was put. Anaesthesia was maintained by nitrous oxide:oxygen [4 :2] and Sevoflurane. As a routine in our setup patients will be premedicated with inj midazolam 1 mg for all those more than 50 kg along with glycopyrrolate and opioid . But in our study , IV midazolam was not given so as to avoid overdosing of sedatives.

Unanticipated difficult intubation cases (more than one attempt or duration> 45 secs) were excluded .Within fifteen minutes after intubation **third blood sample** was taken. At the end of surgery inj Glycopyrrolate 10 mcg/kg and inj Neostigmine 40-70 mcg/kg was

used to reverse residual neuromuscular block and extubated. Immediately within fifteen minutes after extubation **fourth blood sample** was taken after informing the patient. All patients were observed in the recovery room before shifting to the postoperative ward. Along with serum cortisol , plasma glucose and serum prolactin were also measured in the fourth sample.

During the course of the surgery blood pressure and pulse rate were noted down in the anaesthesia management chart maintained by the person giving anaesthesia. On the first postoperative day around 8 .00 AM, when blood was collected for routine investigations, additional 2 ml [**fifth sample**] was taken for the study .

SAMPLE ANALYSIS

All the blood samples were centrifuged immediately and stored at minus 20^0 C till the testing was done .Samples for blood glucose were collected in fluoride tubes and tested as early as possible.

In our biochemistry laboratory serum cortisol and serum prolactin were estimated using Beckman-coulter chemiluminescent hormone analyser. Blood glucose was estimated by Cobos C 3 11 automated analyser .

Blood samples taken for analysis

1. Serum cortisol : Baseline, After Premedication, Post intubation , Post extubation, Postoperative sample after twenty four hours.
2. Blood glucose Preoperative and Postoperative. Serum Prolactin after extubation

FLOW CHART OF EVENTS

PREOP NIGHT: COUNSELLING AND CONSENT / T.RANITIDINE15OMG

ON DAY OF SURGERY:

1ST SAMPLE 8.00AM - FOR SE CORTISOL

1 HOUR BEFORE ORAL PREMEDICATION UNDER SUPERVISION OF STAFF NURSE

CONNECTED TO MONITOR

SHIFTED TO THEATRE IN STRETCHER ACCOMPANIED BY TRAINED PERSONNEL

2ND SAMPLE AFTER SECURING IV ACCESS [PRE –INDUCTION]

IV INJ.GLYCOPYRROLATE,PENTAZOCINE,THIOPENTONE,VECURONIUM

INTUBATION

3RD SAMPLE: **WITHIN 15 MINUTES AFTER INTUBATION**

4TH SAMPLE: **WITHIN 15 MINUTES AFTER EXTUBATION**

5TH SAMPLE: **8.00 AM IN THE FIRST POSTOPERATIVE DAY**

STATISTICAL ANALYSIS

After consulting the statistician the sample size was set at 80 patients. Intial pilot observation showed a 10% difference between the control and the premedicated group.This study was designed to find out the difference between the two premedicants namely T.Midazolam7.5mg and T.Pregabalin 150mg. After thorough review of previous studies approximately 40 patients including 5% for missing values were included in each group inorder to ensure a power of 80% which would permit a type 1 error of $\propto$ =0.05.The results were analysed using SPSS Version 17 software with the help of the statistician.

Normality was checked using Kolmograv Smirnov test and it resulted in a p> 0.005 for almost all the variables which implies that the data are normally distributed. The students paired t-test was used to compare the mean change in the cortisol levels in the two groups. Categorical variables were analysed using Chi Square test . Values that were not normally distributed or when the mean value was less than two times the standard deviation, were analysed with non-parametric statistical methods.

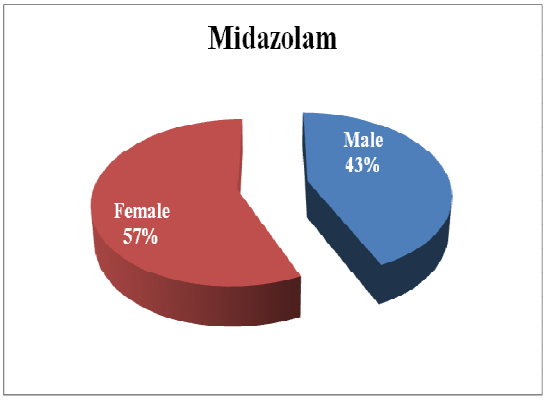
All results were presented as means ± standard deviation. A

p value < . 05 was considered as statistically significant.

Eighty five patients belonging to ASA physical status 1 and 2 were enrolled after getting informed consent and randomly allocated to the two groups. Both groups were comparable in age, gender variability, the type of surgery and the mean duration of surgery.

Table-1 : POPULATION CHARACTERISTICS

GROUP	MIDAZOLAM N=37	PREGABALIN N= 48
AGE (YEARS)	33.45 ± 11.92	31.27± 11.17
SEX (M:F)	16:21	24:24
DURATION OF SURGERY (HRS)	2.17 ± 0.77	2.11± 0.62



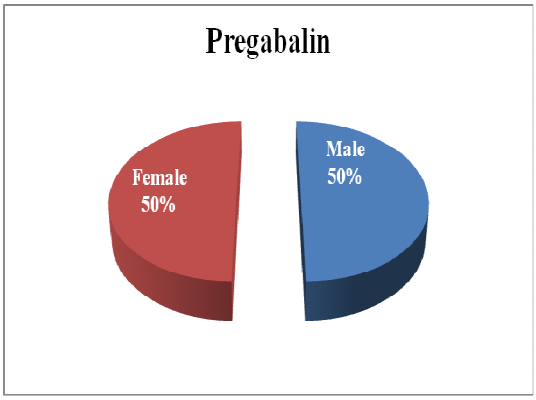


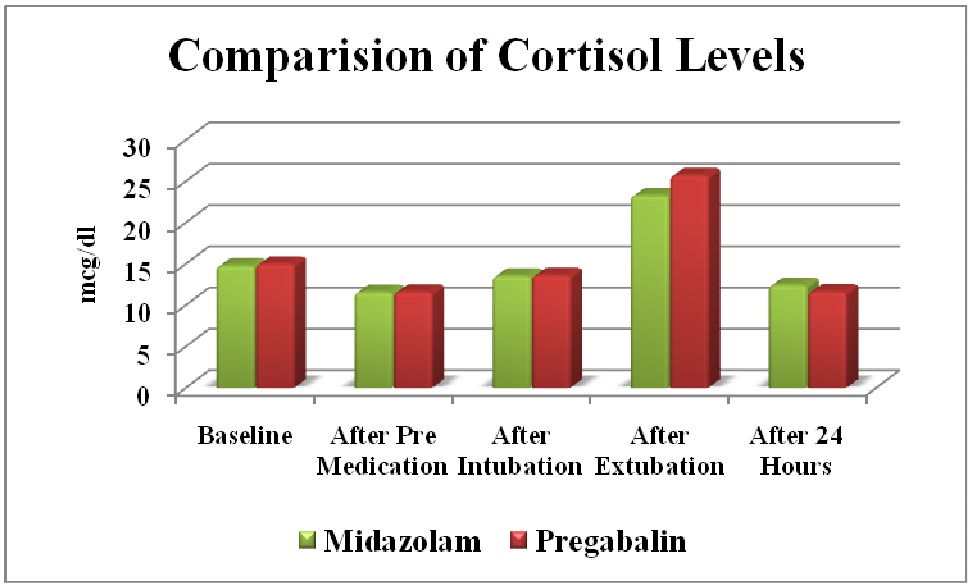
Table 2 : CORTISOL LEVELS IN MIDAZOLAM AND PREGABALIN GROUP

	MIDAZOLAM mean ±sd (mcg/dl)	p value	PREGABALIN mean ±sd (mcg/dl)	p value
C1:C2	14.76±4.4 : 11.56 ± 6.0	p = .002	14.97±7.16 : 11.59± 7.8	p=.014
C1:C3	14.76±4.4 : 13.52 ± 6.7	p = .019	14.97±7.16 : 13.6 ± 6.88	p=.021
C1:C4	14.76±4.4 : 23.26 ± 10.3	p < .01	14.97±7.16 : 25.71±18.3	p<.01
C1:C5	14.76±4.4 : 12.42 ± 3.2	p < .01	14.97±7.16 : 11.63± 5.84	p=.01

C1: baseline cortisol **C2**: cortisol after premedication**,** **C3:** cortisol after intubation **C4:** cortisol after extubation**,** **C5**: cortisol after 24 hours

Baseline cortisol value is the value that is measured in the sample taken around 8.00 A.M. This is the time when the cortisol levels show a physiologic peak. This value is comparable in both the groups. The rest of the values were compared with the respective baseline value.

There was a significant reduction in the cortisol level after premedication when compared to the baseline value in both the groups (Midazolam-p=.002/ Pregabalin-p=.014)



. There was significant difference between the baseline cortisol level and the cortisol level after intubation($p < 0.01$) in both groups. Both groups had almost constant levels of serum cortisol during the surgery with a peak after extubation.

There was a increase in serum cortisol levels after extubation in both the groups which was statistically significant ($p < 0.01$).The mean value after extubation was slightly greater in the Pregabalin group than the Midazolam group.The serum cortisol levels returntobaseline values within twenty four hours after surgery in both the groups.

Table 3: SERUM PROLACTIN

GROUP	POSTOPERATIVE VALUE ng/ml	NORMAL VALUE 2.64 to 13.13 ng/ml	p=ns
MIDAZOLAM	88.22±69		
PREGABALIN	65.18±41		

Both groups did not have significant reduction in serum prolactin.

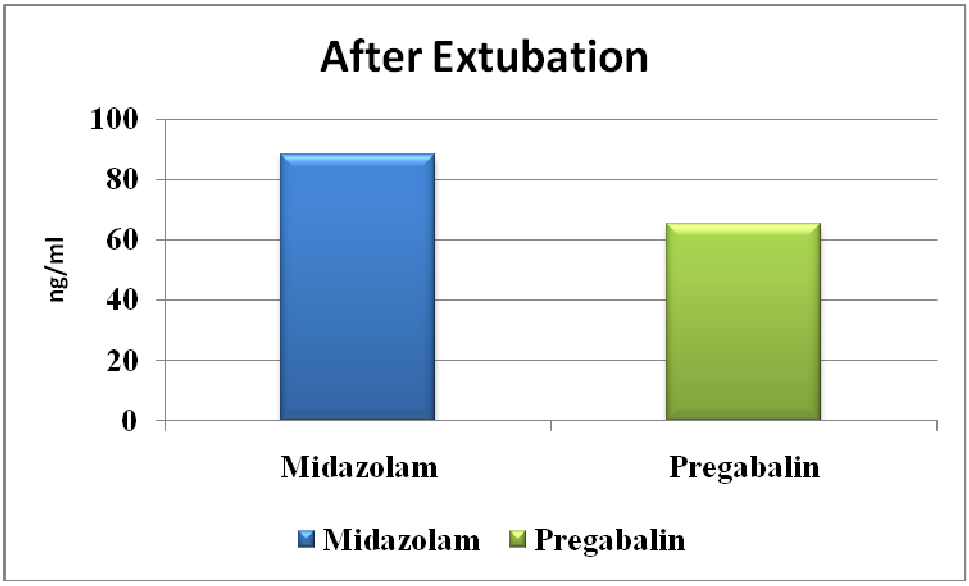
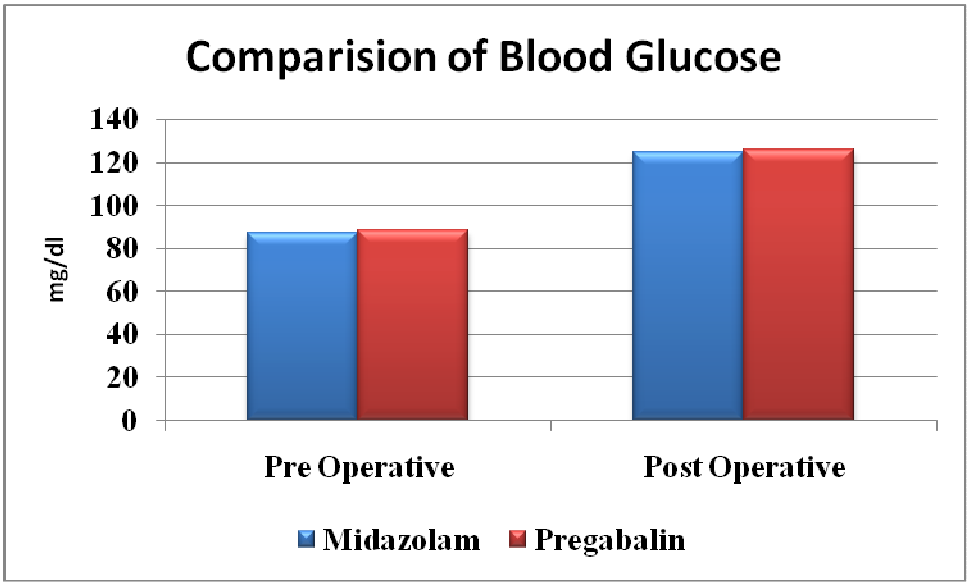


Table 4 : BLOOD GLUCOSE

GROUP	PREOPERATIVE mg/dl	POSTOPERATIVE mg/dl	
MIDAZOLAM	87± 12.38	124.6±37	p = ns
PREGABALIN	88.64 ± 13.62	126.08±33	

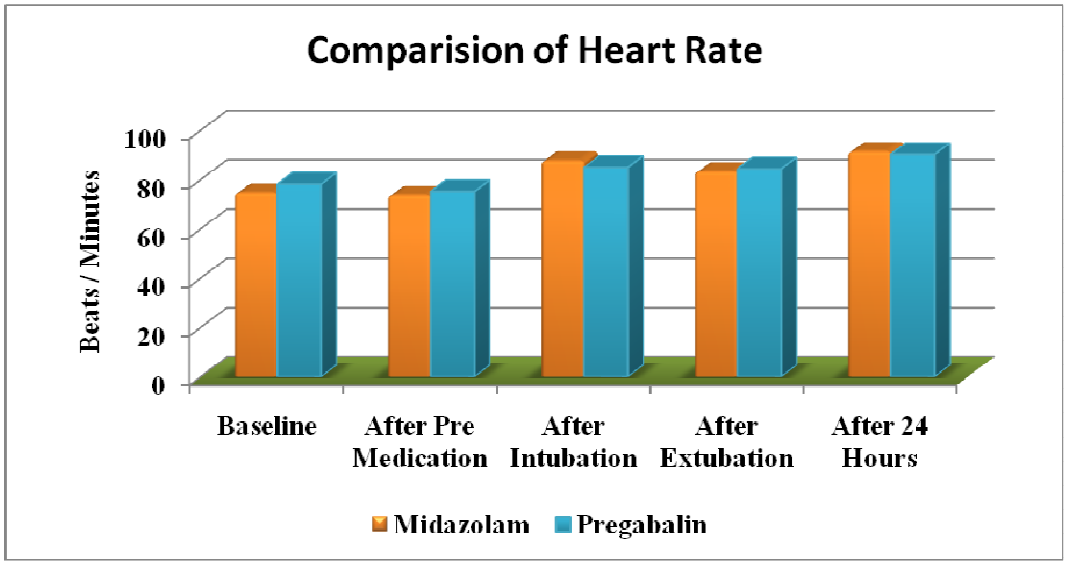
Both the groups did not have significant reduction in the blood glucose levels.



HEMODYNAMIC VARIABLES:

Table 5 : HEART RATE

GROUP	Baseline rate/minute	after premedication rate/minute	after intubation rate/minute	after extubation rate/minute	after 24 hours rate/minute
Midazolam	74.59±8.421	73.59±7.11 (ns)	87.65±128 (p<.01)	83.19±10.3 (p<.01)	91.29±14.6 (ns)
Pregabalin	78.17±10.82	75.21±8.27 (p=.002)	85±12.41 (p=.002)	84.42±11.29 (p=.002)	90.21±12.4 (ns)



In the Pregabalin group, after premedication, there was a significant decrease in heart rate(p=.oo2).

There was significant increase in the heart rate(p=.002) , systolic bloodpressure (p=.001) and diastolic blood pressure (p<.01) after intubation.

There was a significant increase in both the groups in the heart rate(p=.002) , systolic bloodpressure (p=.007) and diastolic blood pressure (p=.002) after extubation.

There was no significant change in the hemodynamic variables after twenty four hours.

In the Midazolam group, there was no significant decrease in the heartrate and diastolic blood pressure one hour after premedication though there was a slight decrease in systolic blood pressure. But there was significant increase in the intraoperative heart rate , systolic and diastolic blood pressure. There was no significant reduction in the hemodynamic variables after twenty four hours

Table 6 : SYSTOLIC BLOOD PRESSURE

Group	baseline mm of hg	After premedication mm of hg	After intubation mm of hg	After extubation mm of hg	After 24 hours mm of hg
Midazolam	114.22 ±11.74	118.27±12.47 (p=.025)	131.35 ± 12.06 (p<.01)	132.62 ± 10.7 (p<.01)	135.35 ± 24.9 (ns)
Pregabalin	118.56± 12.55	114.77 ± 15.01 (ns)	127.48 ± 13.42 (p=.01)	125.56±12.83 (p=.007)	131.30 ± 22.1 (ns)

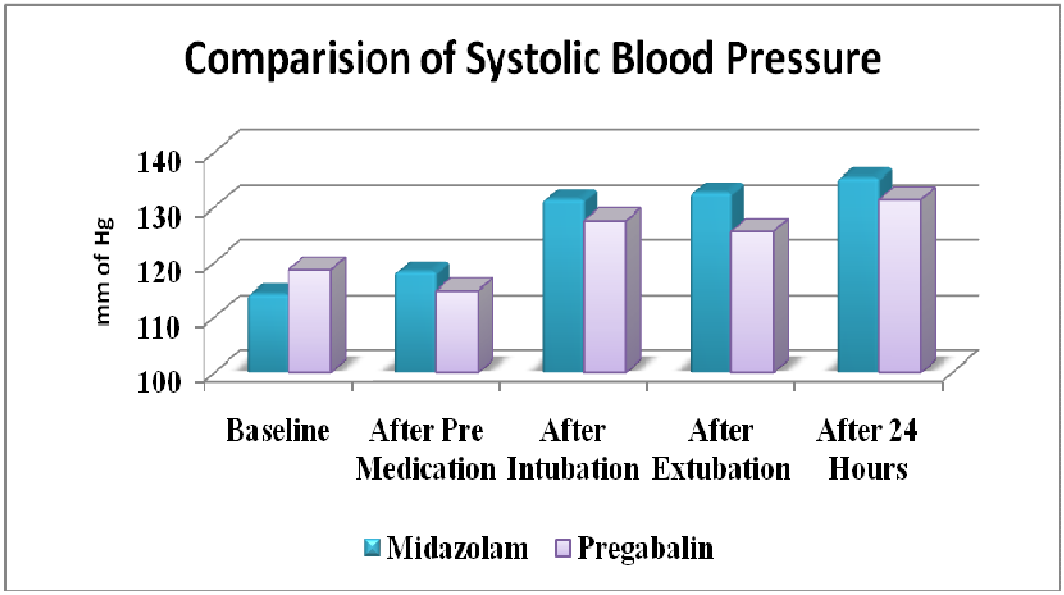


Table 7 : DIASTOLIC BLOOD PRESSURE

Group	Baseline mm of hg	After premedication mm of hg	After intubation mm of hg	After extubation mm of hg	After 24 hours mm of hg
Midazolam	75 ± 9.79	73.03±9.84 (ns)	81.96±10.36 (p=.001)	80.84±12.29 (p=.014)	83.18±11.7 (ns)
Pregabalin	74.31±8.60	71.48 ±9.75 (ns)	83.56±11.34 (p<.01)	80.85±9.20 (p=.002)	86.75±13.08 (ns)

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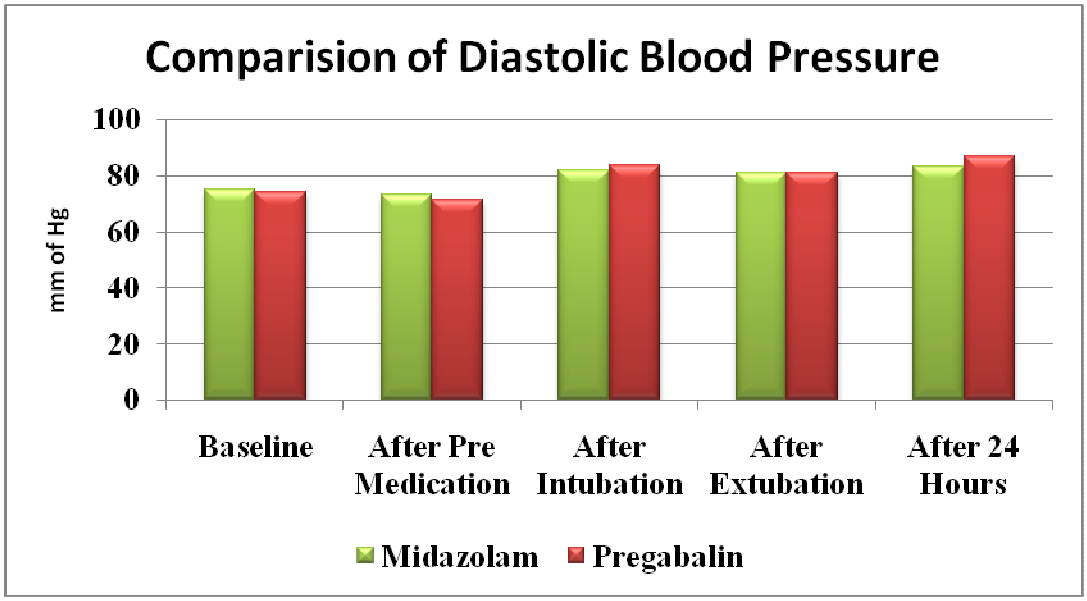
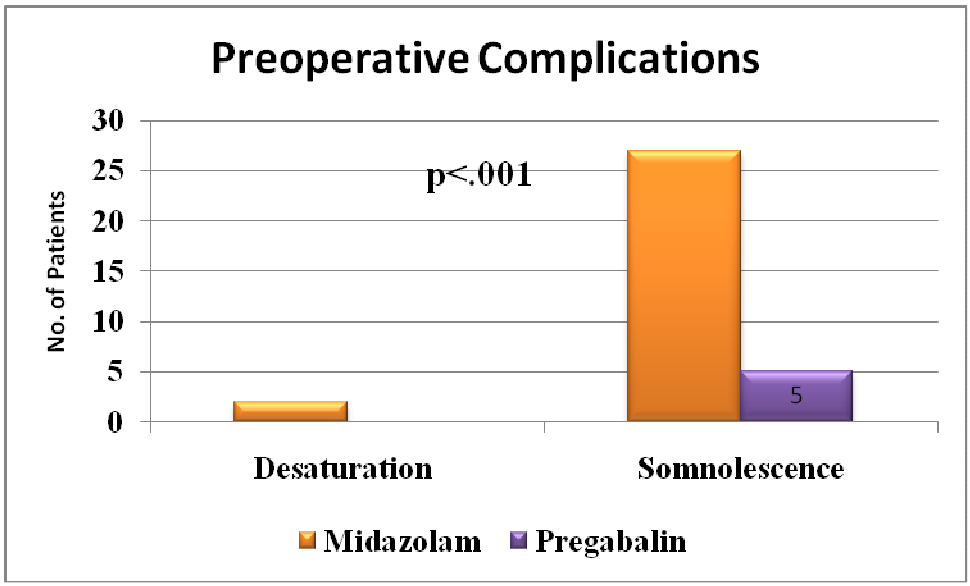


Table -8 PREOPERATIVE COMPLICATION

GROUP	NUMBER	NONE	DESATURATION	DROWSINESS
MIDAZOLAM	37	8	2	27
PREGABALIN	48	43	0	5



In the preoperative period most of the patients in the Midazolam group were sleeping before induction ($p < 0.01$) while only five patients in Pregabalin group were feeling sleepy.

None of them desaturated (i.e.SpO2 < 95%) in Pregabalin while in the Midazolam group two patients desaturated($p < 0.01$). and O2 supplementation was done with Hudson mask in the preoperative room

Table -9 PREOPERATIVE SEDATION

GROUP	1	2	3	4	5	6	
MIDAZOLAM	2	0	0	24	11	0	p=0.001
PREGABALIN	0	29	19	0	0	0	

RAMSAY SEDATION SCORE

1-anxious,restless

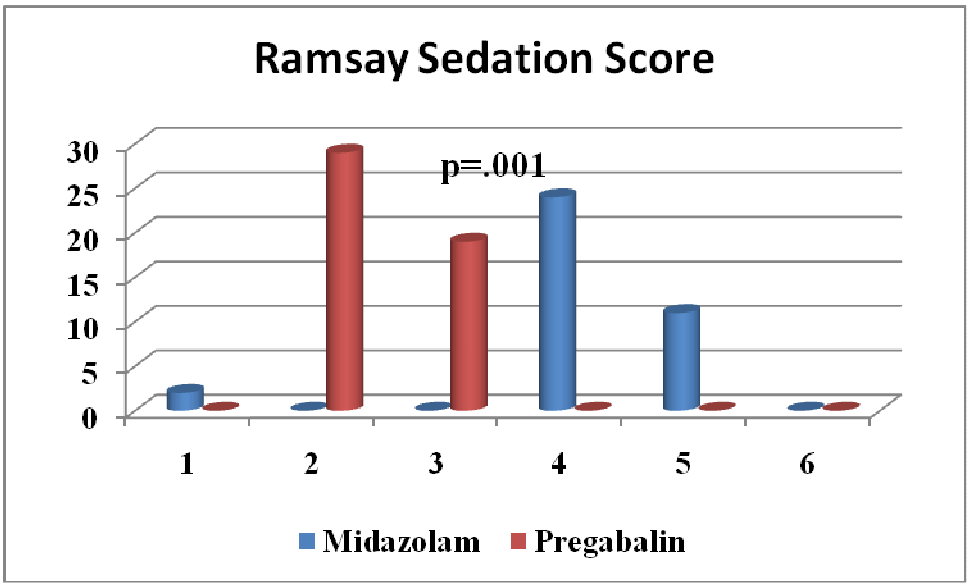
2- Cooperative,tranquil

3- Responds to commands only

4- Brisk response to tap / loud noise

5- Sluggish response to tap / loud noise

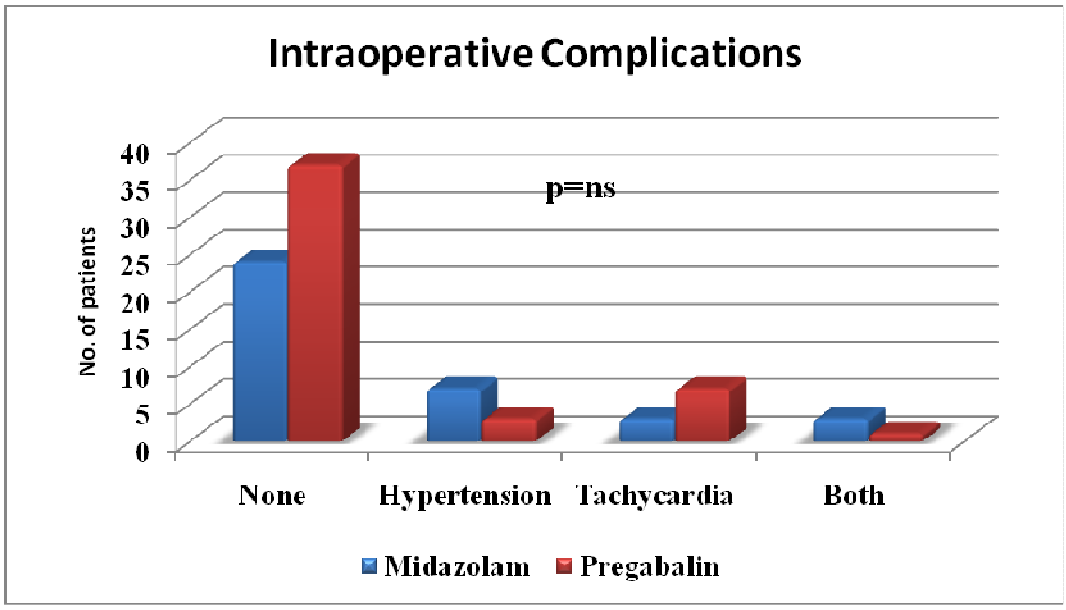
6- No response.



Preoperative sedation was assessed using Ramsay sedation scoring system. Sedation scores were high in Midazolam group than the Pregabalin group ($p < 0.01$). Most of the patients were sedated and were feeling sleepy while they were put on the operating table.

Table-10 INTRAOPERATIVE COMPLICATIONS

	NO	NONE	HYPERTENSION	TACHYCARDIA	BOTH	
MALE	37	24	7	3	3	p=ns
Female	48	37	3	7	1	



There was no significant difference in both groups as far as the intraoperative complications were concerned. In both the groups some of the patients had high blood pressure (more than 20% increase from baseline level) necessitating treatment with nitroglycerine in a dose of 0.5 mcg/kg/min. Some of them were treated with extra doses of inj.Fentanyl 0.5 mcg/kg for tachycardia.

Table-11 POSTOPERATIVE COMPLICATIONS

Group	None	Bucking During Extubation	Postoperative nausea and vomiting	Shivering
Midazolam	25	3	4	4
Pregabalin	40	5	1	2

In the postoperative period the patients belonging to Midazolam group had more nausea vomiting and shivering but our study failed to demonstrate significant difference in both the groups.

In the Pregabalin group patients five patients coughed on the tube. But, this was not statistically significant.

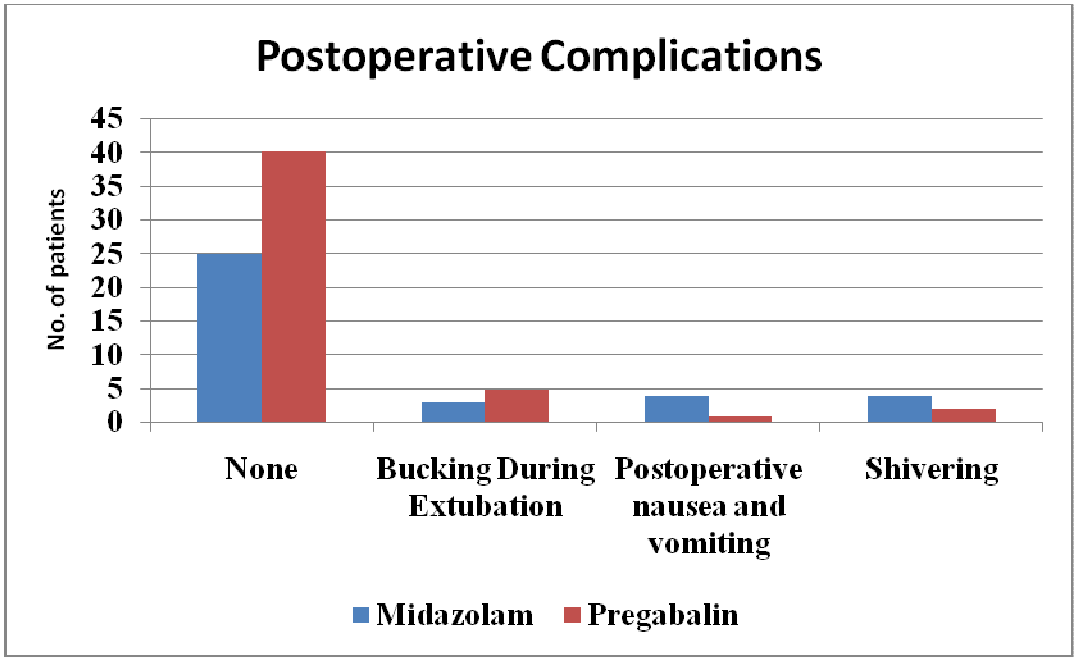
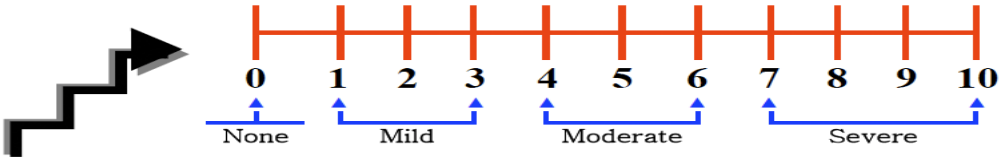


TABLE- 12 POSTOPERATIVE PAIN SCORE

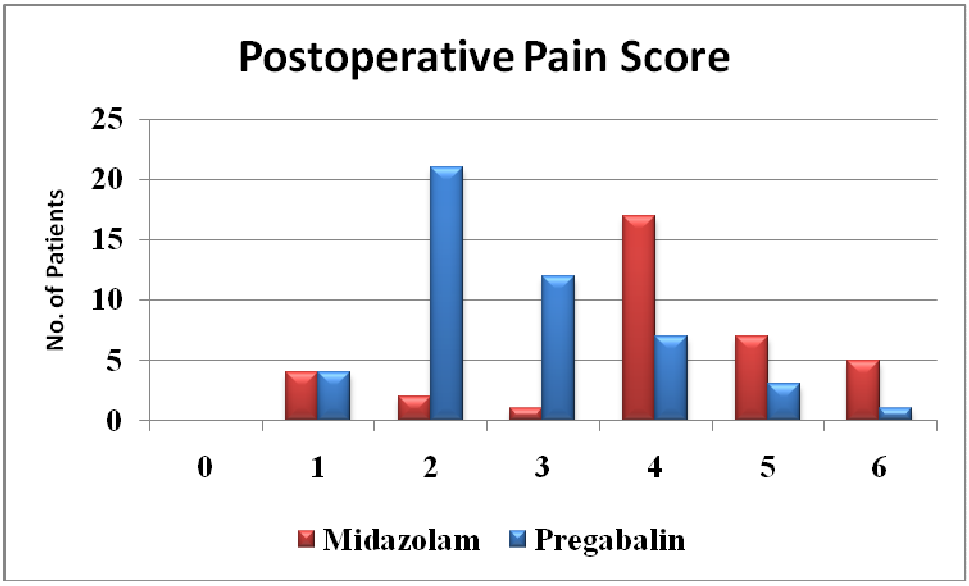
(Numerical rating scale)

group	1	2	3	4	5	6
Midazolam	4	2	1	17	7	5
pregabalin	4	21	12	7	3	1

Numerical rating scale:



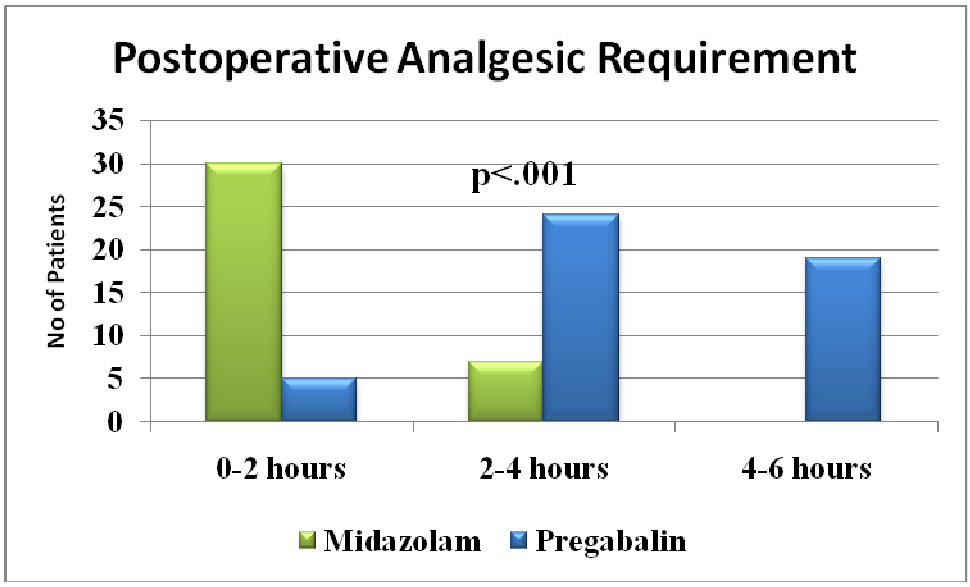
After extubation all patients were asked to rate their pain by looking at the numerical rating scale. All of them were able to understand and give a value to the intensity of the pain.



There was significant reduction in Pregabalin group ($p < 0.01$) than the Midazolam group.The patients belonging to the pregabalin group had a sense of wellbeing and calmness.

Table-13 POSTOPERATIVE ANALGESIC REQUIREMENT

Time after extubation	0-2 hrs	2-4 hrs	4-6 hrs
M	30	7	0
P	5	24	19



Postoperative analgesic requirement was significantly low in the Pregabalin group . (p<..01) but in the Midazolam group most of them needed analgesics within two hours of extubation in the postoperative ward.

DISCUSSION

Our study intended to study the pattern of rise of serum cortisol in response to anesthesia and surgery after premedicating two groups of patients one with Midazolam and another with Pregabalin.

Our results showed that the increase in serum cortisol was blunted by the administration of Midazolam and Pregabalin.This reduction was significant just before and after intubation and was not significant at the end of the surgery and extubation.

The serum cortisol levels were around the baseline after twenty four hours after surgery.This finding is consistent with the study conducted by Barker etal[8.]

The degree of surgical manipulation seems to be play a major role in triggering the neuroendocrine stress reponse as Unase et al [11] in their study rightly said that 'the immunoendocrine response to surgical trauma is dependent on the surgical technique'. The finding in our study was consistent with this observation and the post extubation cortisol values were very high.

In our study we found that serum prolactin levels were very high in both the groups after extubation and both the drugs did not

produce a favourable effect on the neuroendocrine stress response at that point of time.Though serum prolactin levels do not cause major metabolic derangements, it is regarded as a more reliable indicator of the stress response.This is quoted in a study by Riverso et al[5.]

Induction of anaesthesia is a critical phase in the surgical management of patients. The neuroendocrine stress response resulting in increase in the cortisol levels can trigger an array of events which results in undesirable elevations in hemodynamic parameters, altered metabolic derangements leading to protein breakdown, immunomodulation interfering with wound healing. In our study we were able to demonstrate significant reduction in the post intubation serum cortisol values thus proving that both Midazolam and Pregabalin are good adjuvants for smooth induction of anaesthesia .

Most of the studies done with Pregabalin in attenuating stress response compared hemodynamic parameters rather than the hormones. The serum cortisol levels in post extubation phase were high in Pregabalin group than the Midazolam group which needs to be further validated by more studies in future. The heart rate was controlled before induction by Pregabalin efficiently than Midazolam. This makes Pregabalin a good anxiolytic agent. The role of Pregabalin

as an anxiolytic is well showed by Baidiya et al [29] where they say that Pregabalin is effective in the treatment of generalized anxiety disorder. Pregabalin has less effect on the hemodynamic parameters so there was no statistically significant decrease in the systolic and diastolic blood pressure after premedication.

In our study, a decrease in systolic blood pressure before induction was observed in the oral Midazolam group which may be due to mild cardiac depression caused by Midazolam in therapeutic doses.This is consistent with the study done by Heine etal[19] in which they quote that both systolic and diastolic blood pressure decreased significantly in patients treated with Midazolam .

The increase in hemodynamic variables observed in the intraoperative period need not be directly attributed to the neuroendocrine stress response because George et al have concluded in their study that the way in which the body responds to the increase in catecholamines is always not proportional to the catecholamine levels. They also added that cortisol and prolactin estimation are more reliable than the hemodynamic responses in quantifying the stress response.

In our study we found that both Midazolam and Pregabalin failed to suppress serum prolactin levels and prevent hyperglycemia after extubation. The stress hormones are released more in response to surgical manipulation and emergence from anaesthesia and preoperative drugs have got little control over the stress hormones at the end of surgery. Modifying the surgical technique, minimal tissue handling, reducing the duration of surgery may be successful in allieviating the neurohumoral stress response.

Pregabalin seems to be superior in maintaining stable hemodynamics and so it scores well over Midazolam as a premedicant. Our study demonstrated that in the group premedicated with Midazolam there was statistically significant drowsiness ($p < 0.01$) before induction . Ravitsky etal[22] also found that after one hour of oral Midazolam ingestion there was significant reduction in alertness but no adverse events occurred.None of the patients in the Pregabalin group desaturated while two of them did in Midazolam group requiring oxygen supplementation preoperatively..

The patients belonging to Pregabalin group were cooperative, alert, calm, in the preoperative period and a sense of well being prevailed in the postoperative period .The requirement of analgesia

was significantly delayed ($p< 0.01$) in this group in the immediate postoperative period.

But in the intraopertaive period there were complications like tachycardia, hypertension in the both the groups necessitating intravenous infusion of nitroglycerine in the dose of 0.5 mcg/kg/min and additional doses of inj. Fentanyl 0.5 mcg /kg in the postoperative period.

The patients belonging to Midazolam group had more nausea, vomiting and shivering but our study failed to demonstrate statistically significant difference in the incidence of postoperative complications in the two groups.

In our study awakening was prompt in the Pregabalin group though a few of them coughed on the tube. But most of the patients were sleepy during reversal and extubation in the Midazolam group. Kumkum gupta et al[24] in their study have found out that Pregabalin maintained hemodynamic stability and did not cause any respiratory depression, proving to be safe in obese and airway compromised patients.

In our study it was found that almost all the patients had elevated blood glucose level and prolactin levels at the end of surgery. Miller's textbook of anaesthesia says that the postoperative period is the most significant period in causing the stress response. Emergence from anaesthesia and surgical manipulation cumulate to cause a cascade of triggering factors that bring about magnificient changes in the patient under anaesthesia. Our study was consistent with this reference . Both Midazolam and Pregabalin were able to decrease the cortisol level except during the postextubation phase .

SUMMARY

This study was done to assess the pattern of rise of serum cortisol in patients premedicated with Midazolam and Pregabalin. A randomized prospective study was carried out in 85 patients aged between 18 and 55 undergoing general anaesthesia for elective surgeries .Serum cortisol, serum prolactin , blood glucose, heart rate and blood pressure were measured at five times namely baseline, after premedication , after intubation, after extubation, and twenty four hours after surgery.

Our study demonstrated that both Midazolam and Pregabalin were able to reduce the serum cortisol levels before and after intubation ($p < .01$) thus proving to be good premedicants. We also found that both the drugs failed to decrease the neuroendocrine stress response following extubation at the end of the surgery. We found that with its advantageous therapeutic profile Pregabalin proves to be superior to Midazolam in maintaining stable hemodynamic parameters, anxiolysis with out undue sedation and efficient analgesia in the immediate postoperative period.

Oral premedication given one hour before surgery is feasible only in preoperative wards which are far away from the well – equipped theatre suite and trained airway personnel.

Also Pregabalin is found to be safe in hyperreactive airway disease. Pregabalin in the dose of 150 mg is safer than Midazolam in most of the populations and in places with little access to monitors.

CONCLUSION

From this study it is concluded that

Pregabalin in the dose of 150 mg given per orally one hour before elective surgeries can attenuate the neuroendocrine stress response due to induction and intubation .

This dose (150mg) is optimal in that it doesn't cause undue preoperative sedation at the same time provides efficient analgesia in the early postoperative period .

Midazolam is also effective in attenuating the humoral stress response but stringent monitoring is warranted to avoid hypoxemia before induction more so in obese and in patients with respiratory diseases.

Better surgical skills and techniques have got a major role in attenuating neuroendocrine stress response in addition to the conventional anesthetic interventions.

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s.no	NAME	age	sex	type of surgery	group	C1	C2	C3	C4	C5	pro	G1	G2
1	SUMITHRA	27	f	tonsillectomy	P	7.6	5.8	6.4	8.4	6.02	112	106	143
2	PARANTHAMAN	36	m	laminectomy	P	8	8.01	12.6	15	7.56	130	92	129
3	CHINNADURAI	19		lap cholecystectomy	P	23	2.42	6.17	24	6.4	53.2	88	160
4	SIVAKUMAR	38	m	r gynaecomastectomy	P	20	11.9	17.3	15	8.21	26.8	90	94.4
5	ANANADAN	25	m	lap appendicectomy	P	9.8	10.8	11.2	9.8	11.3	32.6	77	126
6	KANNAN	35	m	r monteggia # orif	P	12	15.3	24.6	37	8.4	68.7	90	95
7	BHAVANI	20	f	torticollis release	P	8.3	11.8	10.7	23	6.6	102	100	235
8	LATHA	21	f	lap cholecystectomy	P	33	34.5	31.8	24	5.4	35.3	90	133
9	CHELLAPANDI	48	m	laminectomy	P	3.2	8.2	11.1	96	5.6	96.8	84	116
10	JEYARANI	42	f	chronic abscess neck excision	P	14	5.7	6	21	10.6	81.6	93	138
11	SURESH	35	m	larynx growth excision	P	7.5	6.3	6.2	22	10.1	117	90	108
12	MAHALAKSHMI	23	f	l fibroadenoma excision	P	17	19	15	26	15.2	97.7	78	133
13	GRACE	40	f	lap cholecystectomy	P	9.7	10	8.9	18	8	86.6	90	251
14	BAOERAJ	50	m	l mastoidectomy	P	3.7	3.4	2.8	22	5.6	49.9	78	94
15	MAHALAKSHMI	21	f	cervical node excision	P	15	5.3	8.8	22	26	73.3	92	102
16	GUNAVALLI	27	f	tubal recanalisation	P	17	14	11.5	7.4	15	98.2	88	120
17	RAJESWARI	23	f	l fibroadenoma excision	P	16	3.1	2.4	25	11.5	41.8	84	130
18	RAMESH	32	m	r mastoidectomy	P	20	20.2	12.9	4.1	13	28.5	80	111
19	SENTHIL	22	m	lap appendicectomy	P	20	17.4	17.9	18	15.6	31.2	74	127
20	FATHIMA	32	f	lipoma shoulder excision	P	15	4.04	4.32	4.3	16.1	82.8	90	113
21	PRAMILA	37	f	hemithyroidectomy	P	6.3	6.3	5	5	12.6	171	83	96.8

s.no	HR1	HR2	HR3	HR4	HR5	bp1sy	bp1di	bp2sys	b2dia	bp3sys	bp3dias	bp4sys	bp4diastole	bp5sys	bp5dias	DURATION	SED SCORE	PAIN SCORE	PREOP C	INTRAOP C	postop c	post extu anal
1	78	70	89	80	112	120	86	130	72	150	100	130	80	136	82	1.15	2	1	0	0	0	3
2	86	88	112	104	96	117	80	117	76	140	100	153	86	150	89	3	2	2	0	0	0	3
3	79	66	98	85	108	106	70	106	84	106	90	123	70	153	72	3	2	2	0	0	0	3
4	68	62	74	91	92	104	70	104	83	114	84	126	92	130	80	3	2	3	0	0	0	2
5	71	70	89	81	93	130	74	130	70	150	103	136	82	130	78	2.4	2	2	0	0	0	3
6	68	62	93	85	101	101	80	101	63	120	70	118	68	120	90	1.2	2	3	0	0	0	2
7	90	82	88	71	93	106	60	106	53	137	50	113	73	130	72	2	2	1	0	0	0	3
8	58	68	74	65	83	128	70	128	70	136	82	120	68	140	86	3.1	2	1	0	0	0	3
9	62	66	90	83	81	128	71	128	80	130	100	128	94	136	75	2.3	2	2	0	2	0	3
10	53	58	90	70	81	106	70	106	68	150	100	128	84	130	79	2.4	3	4	0	0	0	1
11	82	80	68	88	72	126	70	126	82	140	86	126	69	136	59	1.4	3	2	0	0	0	3
12	71	81	81	66	85	130	72	130	80	106	76	107	84	130	70	1.5	3	3	0	0	0	2
13	90	82	92	106	65	110	80	110	80	130	86	140	90	120	70	1.5	3	5	0	0	3	1
14	73	66	93	95	68	106	70	130	68	112	72	106	68	140	76	1.2	3	2	0	0	0	3
15	74	78	78	71	80	110	70	96	72	113	70	120	80	104	70	2.3	2	3	0	0	2	2
16	80	81	66	90	81	130	80	108	62	120	80	136	92	130	88	2.2	3	2	0	1	0	3
17	66	65	85	75	74	96	80	100	65	117	78	128	86	130	92	1	2	3	0	0	0	3
18	67	70	71	72	91	108	70	110	70	120	84	126	92	140	100	1.3	3	4	0	0	0	2
19	83	76	75	86	78	100	70	130	72	130	90	134	94	130	80	2.3	2	5	2	1	1	1
20	78	71	78	95	97	110	68	136	70	136	86	156	90	130	76	2	3	2	0	0	0	3
21	72	68	88	98	92	130	80	117	72	117	73	150	98	136	84	1.3	2	2	0	0	0	3

s.no	NAME	age	sex	type of surgery	group	C1	C2	C3	C4	C5	pro	G1	G2
22	RAMU	35	m	discectomy	P	13	15.2	19.1	12	0.8	13.4	91	134
23	HAFEEZAR	54	m	# humerus orif	P	18	27.3	26.8	34	1.8	14.1	95	172
24	VINOTH	18	m	septorhinoplasty	P	17	6.5	6.2	18	15.2	15.1	111	102
25	JAYASRI	18	F	lap appendicectomy	P	14	5.8	20	26	13.6	71.5	31	131
26	amudha	34	F	r mastoidectomy	P	15	8.01	12.3	19	12.7	110	106	156
27	sangeetha	21	F	lap cholecystectomy	P	19	12.42	16.5	32	18.4	54.2	88	92.3
28	rajendran	50	M	r acromioclavicular joint # orif	P	16	11.9	13.3	13	11.2	45	72	132
29	sumathy	39	F	sternoclavicular swelling debridement	P	9.9	10.8	19.3	19	10.4	95.5	102	111
30	mala	30	F	lap appendicectomy	P	36	15.3	25.8	43	29.2	197	90	77
31	anitha	20	F	adenotonsilllectomy	P	21	11.8	28	28	18.6	24.6	85	152
32	renuka	18	F	hemithyroidectomy	P	12	34.8	15.7	20	10.8	92.9	96	125
33	kavitha	25	F	septorhinoplasty	P	13	6.6	10.5	88	10.8	35.9	75	134
34	iyyappan	28	M	lap cholecystectomy	P	8.9	8.2	11.2	42	9.1	60.2	113	92
35	ramu	19	M	# clavicle orif	P	13	5.7	13.9	28	11.3	35.2	98	174
36	babu	21	M	#nasal bone	P	14	6.3	16.8	32	12.7	56.8	77	129
37	meenakshi	30	F	lap cholecystectomy	P	27	19	17.7	44	25.8	25.9	71	143
38	thalapathy	24	M	r mastoidectomy	P	8.2	10	11.6	22	9.3	14.9	106	107
39	NARAYANAN	24	M	# nasal bone	P	10	11	15.7	16	8..6	45.1	115	119
40	PAPPA	52	F	r mastoidectomy	P	5.2	6.4	9	32	6.8	23	76	136
41	YUVARAJ	23	M	lap appendicectomy	P	17	16.8	6.7	17	15.6	14.9	82	100
42	GOPAL	54	M	laminectomy	P	12	14.5	15.9	7.7	8.3	14.1	85	138
43	THIRUMURUGAN	36	M	# r humerus orif	P	9.5	10.8	11.6	14	9.02	45.1	84	101

s.no	HR1	HR2	HR3	HR4	HR5	bp1sy	bp1di	bp2sys	b2dia	bp3sys	bp3dias	bp4sys	bp4diastole	bp5sys	bp5dias	DURATION	SED SCORE	PAIN SCORE	PREOP C	INTRAOP C	postop c	post extu anal
22	75	71	75	82	110	127	68	126	82	126	84	132	78	130	86	2.2	3	5	0	2	0	1
23	82	80	68	90	89	120	80	130	70	130	92	120	60	130	70	3	2	4	0	0	0	2
24	86	81	76	88	79	130	83	105	68	105	78	142	78	150	112	1.4	3	1	2	0	0	2
25	78	76	72	88	92	126	72	130	30	130	82	142	78	150	112	1.2	2	2	0	0	0	3
26	93	94	90	89	95	120	56	105	68	112	76	110	80	126	88	3	2	2	0	0	3	3
27	88	80	78	76	79	130	82	121	74	130	80	120	70	122	80	3	2	3	0	0	0	2
28	76	75	79	88	80	142	80	130	82	126	90	117	80	120	92	2.3	2	2	0	0	0	2
29	103	88	85	90	94	126	90	120	80	132	76	126	71	117	80	1.5	2	2	0	0	0	2
30	93	81	106	96	106	100	92	110	68	116	76	106	84	120	96	2.4	2	4	2	2	3	2
31	86	80	117	107	98	131	70	120	71	122	73	121	70	140	108	1.1	2	4	0	0	0	2
32	82	76	79	75	72	117	73	106	80	112	72	128	82	128	78	2.3	2	3	0	0	0	2
33	80	74	88	86	87	106	82	104	78	130	88	117	80	108	78	2	2	4	0	0	0	2
34	76	72	95	92	83	126	68	124	62	150	92	120	78	112	80	3	2	2	0	1	0	3
35	74	70	93	90	95	124	70	52	68	130	96	112	86	102	88	3	2	3	2	0	0	3
36	83	80	83	85	101	130	72	112	68	120	84	112	78	130	100	2	2	3	0	0	0	2
37	76	75	106	101	108	122	68	104	72	112	86	106	80	112	84	2.5	2	3	0	1	0	3
38	74	80	84	76	72	115	71	106	80	136	92	120	80	126	92	2.5	2	4	0	1	0	2
39	68	72	83	80	81	106	62	123	84	140	84	120	76	140	88	2.5	3	3	0	1	0	2
40	63	64	66	64	86	100	58	101	60	150	112	150	106	156	112	3	3	6	0	3	1	1
41	71	70	83	80	92	126	82	104	78	108	60	112	70	142	78	2	3	2	0	0	0	2
42	73	68	70	62	88	113	70	106	80	112	70	120	84	130	90	2.2	3	2	0	0	0	2
43	82	71	68	66	94	104	68	105	70	120	80	123	89	140	110	2.3	3	2	0	0	0	2

s.no	NAME	age	sex	type of surgery	group	C1	C2	C3	C4	C5	pro	G1	G2
44	KAUSALYA	28	F	lap cholecystectomy	P	8.6	9	5.8	32	7.4	106	88	80
45	SHANTHI	50	F	septorhinoplasty	P	13	14.5	10.9	24	11.1	82.2	90	90
46	VENNILA	19	F	clavicle# orif	P	20	21.3	20.3	44	15.2	84.7	102	122
47	EZHUMALAI	52	M	lap cholecystectomy	P	20	22	18.6	38	18.3	78.1	98	107
48	SURESH	26	M	gynaecomasia repair	P	32	30.9	22.3	49	20.1	57.2	91	141
49	ARUL	43	m	fess	M	5.6	3.1	2.6	9.2	6.8	122	98	200
50	VEERAPPAN	35	m	lap cholecystectomy	M	16	11.2	11.6	27	14.6	23.4	93	110
51	REVATHY	18	f	microlaryngeal surgery	M	16	10.9	9.2	21	13.1	375	76	103
52	SURESH	26	m	r mastoidectomy	M	13	18.1	22.6	30	13	121	72	110
53	VANITHA	38	f	r fibroadenoma excision	M	9.4	3.49	3.91	18	11	273	84	76
54	PRAMILA	27	f	hemithyroidectomy	M	15	6.3	5	18	12.6	171	92	96
55	SHANTHI	45	f	r mastoidectomy	M	10	15.8	20.4	28	11	54.5	87	142
56	SARAVANAN	28	m	lap appendicectomy	M	16	18.4	17.3	31	12.3	46	82	138
57	PARIVENDAN	40	m	r radial head excision	M	9.3	11.8	9.5	34	10.1	50.7	112	146
58	SAMIDURAI	36		lipoma chest excision	M	8.7	12.1	14.8	11	9.5	24.2	104	91
59	LOGANATHAN	46	m	lap cholecystectomy	M	15	19.9	28.4	51	12.9	37.3	89	175
60	SRINIVASAN	42	m	r clavicle# orif	M	15	5.6	15.2	18	12.1	28.8	76	133
61	PARVATHY	20	f	lap cholecystectomy	M	20	26.1	21.3	31	5.6	93	64	82
62	SURESH	33	m	laminectomy	M	22	15.6	24.2	21	12.3	98	82	98
63	NANDHINI	25	f	r vocalcyst excision	M	5.4	3.7	3.1	22	6.2	39.6	78	92
64	RAKESH	19	m	l mastoidectomy	M	15	6.9	6.4	19	13.6	112	82	81
65	PUNITHA	28	f	nasal bone plasty	M	17	7.3	6.9	5.1	14	155	110	110

s.no	HR1	HR2	HR3	HR4	HR5	bp1sy	bp1di	bp2sys	b2dia	bp3sys	bp3dias	bp4sys	bp4diastole	bp5sys	bp5dias	DURATION	SED SCORE	PAIN SCORE	PREOPC	INTRAOP C	postopc	post extu anal
44	86	83	85	81	96	117	68	106	52	130	94	131	92	140	108	1.5	3	3	0	0	0	2
45	88	85	83	80	101	109	72	110	68	150	90	120	73	130	100	2	3	2	0	0	0	2
46	73	72	90	92	121	140	83	130	70	146	78	138	80	150	112	1.8	3	2	0	1	0	2
47	82	90	116	102	112	146	97	140	80	140	82	146	82	140	86	2.1	3	2	0	0	0	2
48	112	92	90	89	96	136	89	130	76	130	84	112	76	126	88	2.2	2	2	2	0	0	3
49	88	70	75	82	96	110	70	120	76	128	88	138	100	152	98	2.3	4	4	2	2	0	1
50	71	66	75	82	93	130	84	136	86	140	70	152	122	138	100	3	4	1	0	0	0	2
51	80	72	91	82	114	122	88	132	74	152	102	132	88	138	84	1	4	5	1	0	3	1
52	62	68	71	68	61	111	63	110	70	106	68	112	82	107	68	3	4	1	2	0	0	2
53	84	86	110	102	94	115	78	118	74	138	98	152	80	140	70	1.1	4	6	2	1	2	1
54	73	83	95	100	97	152	105	138	84	122	92	132	80	150	110	2	4	5	2	0	1	1
55	91	84	90	73	95	100	70	112	62	138	74	143	76	150	92	2	4	4	2	3	0	1
56	92	72	91	82	114	96	68	120	88	146	82	121	66	132	77	2.5	4	5	2	2	0	1
57	80	70	76	67	85	127	69	114	68	134	81	123	72	130	61	2	4	1	2	0	0	2
58	60	67	91	84	82	122	68	139	76	140	96	142	92	140	78	1.2	4	4	2	0	0	1
59	63	70	82	75	78	112	72	117	82	132	88	117	78	102	68	3	4	4	2	0	2	1
60	77	75	79	84	85	122	73	112	64	110	62	134	90	131	72	2.5	4	4	2	0	0	1
61	74	68	70	73	79	98	72	100	62	112	76	132	76	148	100	2.3	5	6	2	3	0	1
62	75	77	96	87	119	118	83	128	69	117	85	134	90	142	98	3	5	5	2	0	0	1
63	85	64	68	71	74	107	68	100	62	127	80	120	76	123	85	1	5	1	1	0	2	2
64	66	64	71	72	76	110	70	96	72	126	84	124	80	124	78	3	5	2	2	0	0	2
65	72	70	71	68	74	100	53	120	65	123	70	130	70	140	90	2	5	3	2	0	3	2

s.no	NAME	age	sex	type of surgery	group	C1	C2	C3	C4	C5	pro	G1	G2
66	NBANUCHANDER	19	m	nasalsinus excision	M	14	4	8.7	9.5	12.8	41.1	104	78
67	MARTIN	45	m	lap cholecystectomy	M	22	7.3	19.7	37	20.5	108	92	231
68	SITRARASAN	51	m	lumbar mass excision	M	15	17.5	16.4	30	13.4	99.4	76	126
69	VITTABAI	58	f	lap cholecystectomy	M	23	16.5	25.1	22	13.8	140	80	130
70	KANAGARAJ	53	m	laminectomy	M	11	4.6	4.01	20	9.8	103	68	120
71	ARUNKUMAR	18	m	nasal bone # reduction	M	9.8	13.2	15.9	12	12.9	114	78	118
72	HELENMARY	23	F	r mastoidectomy	M	21	27	22.3	22	13.2	72.1	80	122
73	SURYAPRAKASH	18	M	fess	M	17	12.3	12.7	28	20.6	52.8	70	136
74	SHANTHI	45	F	thyroidectomy	M	16	9.8	10.7	22	15.2	48.2	72	141
75	MURUGAN	27	M	# r humerus orif	M	15	17.4	16.3	30	11.3	50.3	88	152
76	MURUGALAKSHMI	50	F	r breast mass excision	M	12	13.8	11.6	55	10.2	48.6	92	177
77	GANESAN	28	M	r mastoidectomy	M	18	7.8	17.4	20	16.8	78.1	96	108
78	MURUGAN	33	M	laminectomy	M	17	8.8	8.4	26	16	62.5	101	126
79	SHANTHI	55	F	lipoma axilla r excision	M	16	6	10.7	12	13	60.9	102	134
80	MANI	37	F	r gynaecomastectomy	M	18	13.3	13.7	29	10.2	56.1	110	123
81	SEETHA	22	F	septorhinoplasty	M	12	15.1	17.8	14	10.8	55.3	94	141
82	SATHYA	18	F	r fibroadenoma excision	M	9.4	7.9	7.4	26	8.8	48.1	81	139
83	KALPANA	20	F	l fibroadenoma excision	M	19	8.1	16.7	27	15.1	64.3	79	92
84	AMUDHA	36	F	laminectomy	M	19	14.5	14.8	21	14.3	28.1	83	96
85	JANAKI	33	F	lap cholecystectomy	M	15	6.6	7.6	16	10.3	109	92	140

s.no	HR1	HR2	HR3	HR4	HR5	bp1sy	bp1di	bp2sys	b2dia	bp3sys	bp3dias	bp4sys	bp4diastole	bp5sys	bp5dias	DURATION	SED SCORE	PAIN SCORE	PREOP C	INTRAOP C	postop c	post extu anal
66	68	80	91	88	94	120	86	130	72	150	100	130	80	139	82	2	1	2	0	0	0	2
67	76	72	91	82	105	130	74	146	93	153	100	150	84	146	72	3	4	7	2	3	0	1
68	82	85	117	106	126	135	89	141	91	145	75	157	101	136	100	2.5	5	4	0	0	0	1
69	76	71	80	81	98	120	80	130	70	150	90	146	87	158	68	3	4	5	0	1	0	1
70	83	85	90	88	96	117	80	120	76	140	78	150	82	142	72	3	5	4	0	2	3	1
71	60	63	79	82	99	105	75	116	68	136	70	130	70	148	90	3	4	4	2	2	0	1
72	70	73	81	76	85	100	64	112	80	132	70	126	58	136	90	1.2	5	4	0	0	0	1
73	75	71	88	81	81	98	70	122	40	140	80	136	76	140	88	1	4	6	2	0	0	1
74	62	68	76	70	76	120	85	120	70	119	87	130	70	136	80	1.4	4	4	0	0	3	1
75	65	67	78	72	89	110	71	101	75	130	83	123	79	126	97	1.5	5	4	2	1	0	1
76	79	84	92	86	97	117	77	121	87	138	90	140	76	146	93	1.1	4	5	2	0	0	1
77	76	80	97	85	83	105	77	105	68	117	79	130	88	120	76	2	5	4	2	2	2	1
78	77	83	98	81	72	112	76	98	72	120	80	120	64	118	72	2.4	4	4	2	0	3	1
79	87	88	112	90	74	120	90	114	68	118	75	121	70	130	68	2.1	5	6	2	0	0	1
80	68	72	84	92	98	104	58	120	68	130	70	126	86	138	86	3	4	4	2	2	2	1
81	73	76	93	88	92	120	70	110	70	126	73	130	86	140	90	2.3	4	4	2	0	0	1
82	71	74	106	101	105	110	78	110	70	121	81	132	90	122	74	2.1	4	4	2	0	0	1
83	69	71	84	90	96	120	83	126	70	140	80	136	72	130	86	2	4	4	2	2	0	1
84	77	68	114	104	115	105	68	110	80	134	74	128	60	140	86	2.5	4	5	2	0	0	1
85	73	66	90	83	81	106	70	112	80	130	100	128	94	130	79	2.3	1	6	0	0	2	1

ஆராய்ச்சி தகவல் தாள்

- தங்களின் இரத்தம் பரிசோதனைக்காக பெறப்பட்டுள்ளது.
- நாங்கள் மிடசோலம் அல்லது பிரிகாபலின் என்னும் மாத்திரையை பயன்படுத்தி அறுவைசிகிச்சையின்போது ஏற்படும் உடற்கூறு மாற்றங்களின் வீரியத்தை குறைக்க முற்படும் ஆராய்ச்சியை ESI, KK.Nagar மருத்துவமனையில் நடத்த உள்ளோம்.
- உங்கள் இரத்தத்தின் மாதிரி எங்களுக்கு விலைமதிப்பற்றது.
- உங்கள் இரத்தம் பரிசோதிக்கப்பட்டு அதிலிருந்து கிடைக்கும் தகவல் தற்போது உங்களுக்கு அளிக்கப்படும் சிகிச்சைக்கு இடையூறாக அமையாது.
- ஆராய்ச்சியின்போதும், அதன் முடிவுகள் பிரசுரம் செய்யப்படும்போதும் தங்கள் பெயர் மற்றும் உங்களைப்பற்றிய தகவல்கள் மிகவும் இரகசியமாக பாதுகாக்கப்படும்.
- இந்த ஆராய்ச்சியில் நீங்கள் பங்கேற்பது குறித்து நீங்கள் முடிவெடுப்பதற்கு முழு சுதந்திரம் அளிக்கப்படுகிறது.
- ஆராய்ச்சியின்போது எந்த ஒரு நிலையிலும் நீங்கள் இதிலிருந்து வெளியேறலாம் என்பதை தெரிவித்துக்கொள்கிறோம்.
- ஆராய்ச்சியின் முடிவுகளை நீங்கள் அறிந்துகொள்ளவும், அதனால் நன்மை உண்டாயின் உங்கள் சிகிச்சைக்காக பயன்படுத்தவும் வழிமுறை செய்யப்படும் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

தேதி:

இப்படிக்கு

Dr.----------

INFORMATION SHEET

Your blood sample has been accepted.

We are conducting a study on A Randomised clinical trial comparing Midazolam and Pregabalin as premedicants in attenuating neuroendocrine stress response during General anaesthesia in elective surgeries among patients attending ESI-PGIMSR KK NAGAR and for that your blood sample may be valuable to us.

We are selecting certain cases and if your blood sample is found eligible, we may be using your blood sample to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Date:

Signature of investigator Signature of participant

PROFORMA

Name of the patient: Age: Sex: Wt:

Insurance No: OT: Duration Of Procedure:

Diagnosis: Procedure:

Surgeon: Anaesthetist:

PREOPERATIVE DETAILS

ASA Grade Remarks:

Time	Drugcode

INVESTIGATIONS

Hb	RBS	RFT	Electrolytes	ECG	X-RAY	Others

VITALS

BP	Pulse rate	Resp. rate	SpO_2	Temp

INTRAOPERATIVE DETAILS

I.V Access:

I.V.Premedication:

Induction:

Intubation:

Position:

Maintenance:

N_2O	O_2	Volatile	Relaxant

Intraoperative events if any :

Time & Parameter	O MIN	3O MIN	60 MIN	120 MIN	180 MIN
RR					
Temp					
ECG					
Etco2					
U/O					
IVF					

Reversal and extubation:

Recovery & postoperative period:

alert/ drowsy comfortable/uncomfortable ponv- yes/no pain- yes/no

STUDY PARAMETERS

Time [min]	0	15	30	45	60	75	90	105	120	135	150	165	180
HR/min													
BP mmHg													

Lab values	Baseline	Postpremedication	Post intubation	Postextubation	Post operative
Serum cortisol[µg/dl]					
Plasma glucose					
Serum prolactin					